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Motor function characteristics of adults with late-onset Pompe disease: a scoping review

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Abstract

Background and objectives: Pompe disease is a rare neuromuscular disease caused by a deficiency of the lysosomal enzyme GAA. The late-onset of Pompe disease (LOPD) in adults is characterized by weakness of ventilatory, axial and proximal extremity muscles. These muscle impairments progressively impair various motor functions such as locomotion and postural control. Nearly 87% of adults with LOPD report walking problems and over 80% report instability and falls. Knowledge of these motor functions is now sufficient to provide a clear and comprehensive overview of motor function in adults with LOPD. Therefore, this scoping review aimed to summarize current knowledge about motor function in adults with LOPD. It specifically targeted neuromuscular performance, locomotion and postural control.

Methods: A systematic search in MEDLINE (via PubMed), EMBASE and Cochrane databases was conducted until May 2021. We included studies providing primary data on at least four participants exploring neuromuscular performance, locomotion and/or postural control in adults with LOPD. Risk of bias analysis was assessed using tools appropriate to the study designs; ROB 2.0 for randomized controlled trials, ROBIN-I for non-randomized interventional trials, and NOS for cohort studies and case controls.

Results: The search identified 2,885 articles. After screening, 58 articles were included in the analysis. In these studies, 88% explored locomotion, 83% neuromuscular performance and 3% postural control. This review showed that adults with LOPD have symmetrical weakness, concerning especially the hip and lumbar muscles. Locomotor activities are limited with a distance reduction, spatiotemporal gait parameter modification and an increased pelvic drop and tilt. Balance disorders are also observed especially in the anteroposterior direction.

Discussion: We performed the first review on motor function characteristics in adults with LOPD. Although a significant amount of knowledge was synthesized in this review, our study also highlighted the lack of current research on this topic. Maximal muscle strength was the only neuromuscular performance studied and gait biomechanics and postural control were poorly explored in LOPD. Relationships between the degree of muscle weakness and motor function alterations also remains to be determined in adults with LOPD.

Keyword: *Balance, Gait, Muscle strength, Neuromuscular, Locomotion, Postural control*

List of acronyms

GAA: Acid alpha-glucosidase

LOPD: Late Onset Pompe Disease

ROB 2.0: the Risk Of Bias 2 (Cochrane tool)

ROBIN-I: Risk Of Bias In Non-randomized Studies - of Interventions (Cochrane tool)

NOS: the Newcastle-Ottawa Scale

aLOPD: adults with Late Onset Pompe Disease

MMS: Maximal Muscle Strength

6- MWT: 6 Minutes Walk test

6- MWD: 6 Minutes Walking distance

ERT: Enzyme Replacement Therapy

RCT: Randomized Controlled Trial

NRSI: Non-Randomized Studies of Interventions

MMT: Manual Muscle Testing

WGMS: Walton and Gardner-Medwin Scale

GSGC: The Gait, Stairs, Gower, Chair test

MRC : Medical Research Council

Introduction

Pompe disease, also known as glycogen storage disease type II, is a rare autosomal recessive neuromuscular disease. It is characterized by a deficit of the lysosomal enzyme α -glucosidase, causing an overload of lysosomal glycogen. It leads to dysfunction and destruction of muscle fibers¹ and, consequently, to progressive muscle weakening. Symptoms start in the first months of life (extremely severe infantile form), or during childhood or adulthood with a milder presentation² referred to as late-onset Pompe disease (LOPD). Adults with LOPD (aLOPD) account for more than 90% of all diagnoses of Pompe disease.

During the last 20 years, there has been a surge in studies investigating the degree and within-body distribution of muscle weakness in aLOPD. However, the diversity of Maximal Muscle Strength (MMS) assessment methods and characteristics studied in aLOPD may have biased our understanding of LOPD-related muscle weakness³. An overview of studies is therefore needed to provide an accurate description of muscle weakness in aLOPD.

Muscle weakness due to LOPD progressively impairs various motor functions such as locomotion and postural control². Locomotion is the ability to move in the environment, including performing tasks such as walking or climbing stairs. Walking problems concern 87% of aLOPD who often use gait aids to walk long distances⁴. Locomotor function in aLOPD is often assessed using the 6-minute walk test (6-MWT), although other assessments have been reported in literature. Postural control is another impaired motor function in aLOPD⁵. This function has two components: balance (maintenance of stability against external constraints) and orientation (the organization of body segments)⁶. Over 80% of aLOPD report stability disorders and many report falls⁵. Postural control is also an important aspect of quality of life of aLOPD. Knowledge is now sufficient to provide an overview of what we know on locomotion and postural control in aLOPD.

To date, the reference treatment is enzyme replacement therapy (ERT)⁷, which appears to reduce physiological manifestations in the early years⁸. Some studies have also examined physical therapies such as muscle strengthening⁹. Both ERT and physical therapies appear promising, but their effects on motor function remain variable between studies¹⁰. A synthesis of studies examining the effects of ERT and/or physical therapies on motor function is needed to improve knowledge about the management of aLOPD.

Here we propose the first scoping review on motor functions in aLOPD. The following research questions were formulated:

- 1) What assessments have been used to study motor functions in aLOPD?
- 2) What is currently known about motor functions in aLOPD?
- 3) What are the effects of therapies on motor functions in aLOPD?

Methods

Protocol and registration

A scoping review was performed following the guidelines of the Joanna Briggs Institute¹¹. This protocol was registered in Open Science Framework “<https://osf.io/4n98g>” in March 2021. The PRISMA-ScR checklist is included in eAppendix in the Supplement.

Data Availability

Additional data not published within this article will be made available by request from investigators.

Standard Protocol Approvals, Registrations, and Patient Consents

Ethical approval was not required due to the study nature (no human or animal patients).

Eligibility criteria

Inclusion Criteria

To be included, the studies had to target adults with LOPD. We included any randomized controlled trial (RCT), non-randomized intervention study (NRSI), cohorts, case-control, and cross-sectional studies producing primary data on at least four participants. Regarding study intervention, we included all studies that aimed to describe neuromuscular performance, locomotion, postural control, that aimed to compare aLOPD to a control population or that evaluated therapies aimed at improving motor function in aLOPD. There was no restriction on publication dates.

Exclusion Criteria

Literature reviews, unpublished work, conference abstracts, and any study in a language other than English or French were excluded. Studies that were not relevant to answer our objectives and that only briefly mentioned or referred to motor function were excluded.

Information sources and search strategy

MEDLINE, Embase, and Cochrane databases were searched for studies published before 30 May 2021. Search strategies were developed with an experienced methodologist (CW). The most relevant thesaurus keywords were used: Pompe disease, late onset, locomotion, neuromuscular, postural balance. These keywords were combined (with AND/OR) with free words to broaden the search field. Full equations are displayed in the eMethods in the Supplement.

Study selection and synthesis

Article selection was performed by two independent blinded reviewers (TM, TC) in two steps: (1) screening based on titles and abstracts; (2) selection based on full texts. Conflicts regarding data inclusion were resolved by consensus with a third reviewer (CB). Two investigators independently extracted the following data: authors, publication year, country of origin, aims, study population, methodology and design, outcomes and details, and key findings related to the scoping review questions.

Risk of bias analysis

The risk of bias analysis was assessed independently by two investigators (TM, TC) using tools appropriate to the study designs: ROB 2.0 tool for RCTs, ROBIN-I tool for NRSIN and the NOS for cohort studies and case controls.

Results

Selection of sources of evidence

The search identified 2,885 articles. After selection, 58 articles were considered suitable for inclusion in the analysis (Figure 1). Publication dates ranged from 1998 to 2021. Of the studies, 88% (n=52) explored locomotion, 83% (n=48) neuromuscular performance and 3% (n=2) postural control (eTable 1 in the Supplement). The number of participants in each study ranged from 4 to 197. In the 58 studies, 75% of the aLOPD were treated with ERT.

A complete reference list of the articles included is displayed in eAppendix 2 in the Supplement.

Synthesis of results

1 State of knowledge on neuromuscular performance

1.1 *Neuromuscular performance assessment*

Neuromuscular performance assessment can include various aspects such as MMS, explosive strength, power or fatigue. However, most studies only assessed MMS. Manual muscle testing (MMT) was based on the 6-point scale (0–5), which was used in 32/48 studies (Table 1 and eTable 2 in the Supplement). Instrumented assessments were conducted using various devices: hand-held dynamometers (17/48), strain-gauge dynamometers (quantitative muscle test, 5/48), and the gold standard, isokinetic dynamometers (3/48). The Quick Motor Function test, assessing overall MMS in 16 functional activities, was used in 7/48 studies. Neuromuscular fatigue, power, and explosive strength muscle power have never been studied in aLOPD.

Lower limb muscles assessment (41/48 studies) included mostly knee muscles, then hip muscles and finally ankle muscles, with only 8/41 studies using instrumented tools. Upper limb muscles assessments (31/48 studies) included mostly elbow muscles, then shoulder muscles, with 16/31 studies using instrumented tools. Trunk muscles were assessed in 15/48 studies. Eight studies were unclear about which muscles were assessed (eTable 3 in the Supplement).

1.2 *Neuromuscular impairments*

Muscle weakness, the main complaint in aLOPD^{3,4,12}, corresponds to MMS deficits. Although studies reported high variability between aLOPD², a typical pattern is classically described. Weakness is symmetrical³ with lower limb muscles more affected than upper limb muscles. Compared to healthy individuals, aLOPD have a loss of more than 60% of MMS in their leg muscles^{13–15} but only 30% in their arm muscles^{13,15}. Furthermore, weakness concerns more proximal than distal muscles. Van der Beek et al.³ showed that more than 80% of the 97 aLOPD studied had severe hip muscular impairments, while 55% of them had knee weakness and only 10% had ankle weakness. More specifically, if we rank muscles from the most affected to the least affected, we find hip adductors^{3,16}, lumbar extensors³, hip extensors¹⁶, knee and hip flexors^{3,17}, knee extensors³ and ankle muscles¹⁸.

MMS was shown to be significantly inversely correlated with intramuscular fat infiltration measured by magnetic resonance imaging. These correlations were high for lumbar extensors and moderate for other muscles¹⁹.

MMS decline over time in untreated individuals remains poorly explored, and unbiased natural history studies are no longer possible.

Indeed, since the introduction of ERT, most aLOPD are now treated at diagnosis. Untreated aLOPD are mostly mildly affected, with a very slow progression, or have a concomitant severe disease. MMS was only examined in five cohort follow-up studies^{3,12,15}. Authors reported annual impairments ranging from 1.3%³ (MMT) to 7%¹⁵ (strain-gauge dynamometer) on sum muscle scores. Lower baseline MMS and longer time since symptom onset were the best predictors of greater deterioration at 1 year¹⁵. Residual enzyme activity and age of onset did not predict degradation^{3,12,15}.

1.3 Effect of therapy

1.3.1 Effect of ERT

Effects of ERT on MMS was explored in 16/47 studies. Fifteen uncontrolled studies reported significant improvements in MMS during the first three years of treatment^{8,14,20}. The RCT “LOTS”⁷ explored ERT efficacy on MMS in 90 aLOPD (disease duration: 9.3 years). After 1.5 years of treatment, hip adductors, knee flexors and extensors MMS showed no significant difference between treated and untreated patients.

After the first 3 years of ERT, most follow-up studies reported stabilization or even a decline in MMS. Indeed, Haarlarm et al.¹⁴ showed that after an initial improvement, knee flexors and extensors MMS progressively decreased until they were lower than at the baseline after 10 years of ERT (-7.5%). Pena et al.²¹ evaluated the effects of the latest generation of ERT in 21 aLOPD. The authors reported no change in MMS (hip, knee or ankle) after 27 weeks.

1.3.2 Effect of physical therapy

Three studies explored physical therapy effects on MMS^{9,22,23}. Terzis et al.²² proposed a 20-week training program to five aLOPD. It consisted of upper and lower limb strengthening and stretching to be carried out 3 days a week. Hip extensors MMS assessed by a quantitative muscle test significantly improved (+51%), while knee extensor MMS did not change significantly. Van der Berg et al.⁹ proposed a strengthening and endurance exercise program to 23 aLOPD. After 12 weeks, MMS from hand-held dynamometer of hip flexors and shoulder abductors had improved significantly (+15.5% and +5.3%, respectively). In a randomized crossover study, Sechi et al.²³ compared a 26-week strengthening program alone to a 26-week program combining strengthening and diet in 13 aLOPD (baseline of Walton Gardner Medwin Score WGMS: 3.2). Elbow and knee flexors/extensors MMS using an isokinetic dynamometer did not significantly change in either program.

2 State of knowledge on locomotion

2.1 *Locomotion assessment*

Locomotion assessment in the included studies can be separated into three approaches: walking capacities, locomotion performance and gait characteristics (Table 1 and eTable 2 in the Supplement).

The first approach, concerning walking capacities, relates to walking independence (functional abilities and assistive devices). The WGMS, used in 14/52 studies^{24,25}, assesses walking or climbing stairs (8 grades). Other studies described the quality of mobility (unable, able with aids, able with a waddling gait, normal)²⁶ and reported the use of assistive devices⁴.

The second approach, concerning locomotion performances tests using the 6-MWT (44/52), the 10 meters walking test (20/52), the time to climb 4 steps (19/52) and the Timed Up and Go test (5/52). The Gait, Stairs, Gower, Chair test (GSGC) which assesses the capacity and timed performance of five activities (walking 10 meters, stair climbing, rising from the floor and rising from a chair), was used in 14/52 studies²⁷.

Gait characteristics (third approach) involves biomechanical assessments including spatiotemporal, joint kinematic and kinetic gait parameters. Only 3/52 studies²⁸⁻³⁰ analyzed the biomechanical gait parameters of aLOPD. Two case series focused on spatiotemporal gait parameters^{28,29}. Only one study compared the spatiotemporal, joint kinematic and kinetic gait parameters of 12 aLOPD and 12 control subjects³⁰.

2.2 *Locomotion Impairments*

Impairments were found in all studies exploring locomotion in aLOPD^{4,26}. Favejee et al. observed that only 18% of 107 aLOPD walked without assistive devices and with a “normal gait”²⁶. Age, disease duration and ventilator use were the factors that worsened abilities. In their follow-up of 126 aLOPD, Laforet et al. reported that 90% had significant difficulty climbing stairs and 83% had difficulty rising from a chair⁴. Proportion of aLOPD that was using assistive devices ranged from 24%⁸ to 54%³¹. The loss of ambulation leads to 30-50% of aLOPD to use a wheelchair 10-15 years after diagnosis³¹.

Regarding locomotor performance, aLOPD have a reduced 6-minute walking distance (6-MWD) compared to controls. 6-MWD ranged from 49.1% to 71.3% of predicted normal values. In the largest cohort (n=197)⁸, aLOPD had a mean walking distance of 58.4% of predicted values. aLOPD were significantly slower than healthy adults, and had a waddling gait resulting

in a positive Trendelenburg sign². Three studies provided descriptive measurements of the spatiotemporal gait parameters in aLOPD^{28–30}. Authors reported a decreased gait speed^{29,30}, cadence^{28–30} and step length^{28,29}, and an increased double stance time²⁸ compared with matched norms. Only one study reported a statistically significant decrease in speed (1.1 vs. 1.3 m/s), cadence (105 vs. 113 steps/min) and step width (9.9 vs. 12.6 cm) compared with matched controls³⁰. This study reported alterations in gait kinematics and kinetics with greater thoracic sagittal sway (6.0° vs. 3.1°), sagittal pelvic range of motion (6.1° vs. 3.4°), frontal pelvic range of motion, hip adduction peak (10.9° vs. 6.9°), lower hip and knee extension moments (-36% and -12% respectively) and maximum hip generation power (-33%) in aLOPD compared to controls.

2.3 *Effect of therapy*

2.3.1 Effect of ERT

The effect of ERT on locomotion was investigated in 30 studies. Most studies reported significant improvements in 6-MWD. The RCT “LOTS”⁷ showed the efficacy of ERT on 6-MWD and demonstrated significant differences between treated (+25.1 m) and untreated (+3.0 m) aLOPD. However, more recent studies evaluating the long-term benefit of ERT have shown a ceiling effect of this treatment^{8,14}. These studies highlighted a slow decline of 6-MWD after 3 years of ERT. Indeed, after 10 years of ERT, Haarlal et al.¹⁴ found that the average 6-MWD was lower than at baseline (-22%). Regardless of the treatment duration, no change was found in 13/16 studies for the WGMS^{32,33}, time to walk 10 m^{8,32,34,35}, time to climb four steps^{8,32} or the GSGC^{20,21}. Only 3/16 studies reported significant improvements in these capacities and performance tests. In 40 aLOPD, Angelini et al., reported significant improvements in time to climb 4 steps (5.2s vs. 5.8s) and time to walk 10 m (9.9s vs. 12.1s) after 1 year of ERT²⁷. Bembi et al. reported an average gain of more than 2 levels on the WGMS after 3 years of ERT in 17 aLOPD²⁴. In an RCT, Koelberl et al.³⁶ explored the benefits of a novel combination of ERT and Clenbuterol over 1 year. Only the test group improved significantly on the GSGC.

No studies evaluated the effects of ERT on biomechanical gait parameters.

2.3.2 Effects of physical therapy

Three studies investigated the effects of muscle-strengthening programs on gait abilities in aLOPD^{9,23,25}. Van der Berg et al. compared the effects of ERT with or without an associated training program (three strengthening and endurance training sessions per week for 12 weeks)

in 23 aLOPD⁹. Authors reported a significant increase in the 6-MWD (+16 m) and a decrease in the time to climb four steps (-0.3 s after physical training and ERT). No change was observed in the time to walk 10 meters.

In 13 aLOPD, Sechi et al.²³ found no significant change in 6-MWD and other performance tests after a strengthening program alone compared to a combined strengthening and diet program. Slonim et al.²⁵ evaluated the effects of an aerobic program combined with diet on the WGMS (baseline of 3.2) over a 10-year follow-up. The 22 most compliant patients in this program showed a significantly slower deterioration of locomotor function (-29%). No change was observed in the 8 least compliant patients.

3 State of knowledge on postural control

3.1 *Postural control assessment*

Only two studies have investigated postural control in aLOPD and these studies only examined balance^{29,37}. Orientation has never been explored in aLOPD (Table 1 and eTable 2 in the Supplement).

Valle et al.³⁷ assessed standing balance using a force platform in five adults with LOPD and five matched controls. Three foot positions and two eye conditions were studied. A single recording of 50 seconds was performed for each condition. Authors analyzed the center of pressure parameters with the 95% confidence ellipse area and the variability of sway values.

Schneider et al.²⁹ studied standing balance in 16 aLOPD using force platforms. Experiments were conducted under three independent conditions: three head positions, two eye conditions and two conditions with foam pads under the subjects' feet. A 32 seconds recording per trial was performed. Forefoot to hindfoot weight distribution, right/left weight distribution and sway intensities were analyzed.

3.2 *Balance Impairments*

aLOPD frequently report standing balance difficulties, leading to falls and limitations in their functional activities⁵.

Valle et al. and Schneider et al. reported impaired balance in nearly 83% of aLOPD^{29,37}. Although the study by Valle et al. was based on a small sample size, it reported that the amount of postural sway and the variability of postural sway is approximately double aLOPD (n=5) compared to controls (n=5)³⁷. These differences were observed with feet in different positions,

with a significant worsening of sway in the anteroposterior direction and with eyes closed. Schneider et al.²⁹ reported that 9/16 (53%) aLOPD had more anterior weight distribution than controls. They confirmed that these alterations were more pronounced with eyes closed. They also found a correlation between knee MMS and forefoot–heel ratio.

3.3 *Effect of therapy*

No study has evaluated the effect of therapy on balance in aLOPD.

4 Risk of bias of included studies

The risks of bias of the included RCTs, NRSIs, cohorts, and case-control studies are shown in Figure 2, 3, and 4. The included RCTs had a moderate risk of bias due to age differences between the groups and potential conflicts of interest of investigators. The majority of the NRSIs had a moderate risk of bias due to potential confounding, outcome measurement bias, and 22 could have had possible investigator conflicts of interest. Four studies had serious risks of bias. Of the five case-control studies, 4 had allowed to moderate risk of bias and 1 had a high risk. Of the 11 cohort studies, 10 had a low to moderate risk of bias, one had a high risk and 8 could have had a possible conflict of interest of the investigators.

Discussion

This scoping review provides an exhaustive overview of the literature on motor functions in aLOPD and demonstrates that the literature primarily focuses on muscle weakness rather than on locomotor capacities. Little attention has been paid to gait biomechanics nor postural control. Furthermore, little evidence exists about the efficacy of therapy on motor functions due to the lack of RCTs (Figure 5).

Neuromuscular performance: current knowledge and future challenges

Most studies focused exclusively on MMS. Almost 70% of these studies used MMT, which is simple and quick to assess MMS. However, MMT has been strongly criticized due to its lack of sensitivity and reliability^{12,38}. It has been shown that a fixed MMT grade corresponds to a wide range of absolute values³⁸. Only 40% of the studies used instrumented tools, which are more reliable and sensitive to change^{12,17}.

The gold standard for MMS testing is the isokinetic dynamometer due to its metrological qualities^{38,39}, it allows accurate and reliable MMS assessments. Thus, it should be used to assess

the effects of therapies on MMS in aLOPD. Moreover, it can be used to safely strengthen the muscles of aLOPD. Although its use is strongly recommended in aLOPD^{12,14,17}, to date only 18% of studies have used it.

Regardless of the assessment method, all studies showed that muscle weakness is symmetrical and more proximal than distal³. Muscle weakness is significant in hip adductors, lumbar extensors, hip extensors¹⁶ and knee flexors⁴⁰. Knee extensors are less affected, while ankle MMS is preserved. However, few studies have specifically targeted the weakest muscles in aLOPD. Indeed, only five studies have specifically assessed the hip adductors using dynamometers. It is necessary to evaluate MMS of the most affected muscles to have a good view of the MMS deficits and to propose efficient therapies. A low initial MMS and a long delay since onset of the first symptoms are predictive of a more severe decline in MMS and motor functions^{3,12,15}. These factors should alert clinicians to the future course and improve prevention of muscle degradation.

The effect of ERT on MMS has been explored in several studies. Although some NRSI reported a benefit on MMS during the first 3 years, the RCT “LOTS” consisting of a large sample of aLOPD contradicted these results⁷. The authors showed no significant change in MMS over a 1.5-year follow-up in aLOPD treated and untreated with ERT. These results were confirmed in a recent meta-analysis including 413 aLOPD¹⁰. Surprisingly, the effectiveness of muscle strengthening of aLOPD has received little attention in the literature^{9,22,23}. Two studies showed strength gains after muscle strengthening interventions in lower limb muscles^{9,22}. A third study which was an RCT found no effect of a 26-week strengthening intervention knee muscles²³. They suggested that the aLOPD included (n=13) were too weak for their program to be effective. To date, no study has proposed to combine ERT with a muscle strengthening intervention despite the great potential of their combination for the improvement of motor function and quality of life of aLOPD. RCTs that assess this therapy combination with reliable and accurate tools are therefore necessary.

MMS is the only neuromuscular performance studied in aLOPD. Other performance characteristics such as explosive strength has not been studied in aLOPD. Despite the fact that it is i) better related to daily functional tasks and motor skills and ii) more sensitive in detecting changes in neuromuscular function than MMS³⁹.

Experienced fatigue is a common complaint reported by aLOPD. This fatigue could have several origins (muscular, central, respiratory) like other neuromuscular diseases. Neuromuscular fatigability has never been explored in aLOPD⁴¹. Future studies should explore this in aLOPD using methods to distinguish neural and muscular components⁴². These methods typically include repeated or prolonged fatiguing muscle contractions, as well as pre-and post-assessment, including maximal electrically-induced and voluntary contractions. This contribution of knowledge could guide therapy by targeting the mechanisms of this fatigability if it is impaired in LOPD.

Locomotion: current knowledge and future challenges

More than 80% of aLOPD have locomotor limitations^{4,5,8,28}. Indeed, aLOPD have a reduced walking distance and were almost three times slower than healthy controls in performance tests^{16,35,43}. The disease progression increases dependence on assistive devices^{5,15} and 40% of aLOPD used a wheelchair ten years after diagnosis. Most studies only explored walking performance and mostly used the 6-MWT. This global test is not specific to a motor ability because it depends on muscular and cardiorespiratory capacity. However, as the disease progresses, these functions deteriorate in aLOPD, which limits the clinical interpretation of this test⁴⁴. Other reliable and specific methods should be used to improve the understanding of locomotor limitations. For example, the use of inertial sensors has been used for an ecological home-based gait analysis in Duchenne muscular dystrophy⁴⁵.

While aLOPD often have a specific “waddling” gait, only three studies have analyzed biomechanical parameters in aLOPD^{28–30}. Authors confirmed a lower speed and a smaller step length and width compared to controls. These spatiotemporal gait characteristics could be related to the joint kinematic gait parameters. Starbuck et al. highlighted the biomechanical characteristics of this waddling gait using three-dimensional analyses³⁰. The authors noted an increase in pelvic drop, hip adduction and an increase in anteroposterior pelvic tilt and thoracic sway in aLOPD compared to healthy controls. This gait pattern is linked to the MMS degradation. Specifically, hip abductor, lumbar extensor and hip flexor weakness could induce anteroposterior pelvis tilts. However, the diversity of compensations observed supports the muscle damage heterogeneity observed on imaging^{16,34,46}. Although, no study has linked MMS to gait biomechanics parameters. Study of the relationship between gait biomechanics and MMS obtained from reliable tools is necessary. It would identify the muscles that contribute to locomotor limitations and detect sensitive clinical biomarkers that would be valuable in aLOPD follow-up. This would allow clinicians to tailor therapy to improve walking ability and recommend

assistive devices. To date, most studies evaluating the effects of ERT or physical therapy on locomotion have shown a significant but temporary improvement in performance. We suggest testing the efficacy of a combination of strengthening exercises, high-protein diet and ERT to improve locomotor function and quality of life of aLOPD. The use of reliable instrumented tools such as three-dimensional analysis systems would allow the identification of change-sensitive locomotor biomarkers in the context of the upcoming arrival of promising new therapies for aLOPD.

Postural control: current knowledge and future challenges

Affected muscles in LOPD have a key role in balance control. Their alterations seem to strongly contribute to balance disorders and the high risk of falls in aLOPD⁵. Therefore, balance assessments have been strongly recommended by a LOPD expert consensus since 2012⁴⁷. However, only two studies have assessed balance in aLOPD without exploring orientation^{29,37}. These authors found a greater amplitude and variability of postural sway in aLOPD compared to controls. However, these studies had some limitations (only one balance test trial was performed by the participants, whereas 3 trials are recommended⁴⁸) and small sample sizes (n = 5 versus 5 controls³⁷ and n = 16²⁹). It appears essential to systematically assess postural stability in aLOPD, using reliable tools such as force platforms and standardized methods. This would improve knowledge of balance disorders and guide rehabilitation in aLOPD.

The relationship between muscle impairments, balance disorders and risk of falling is explored in some neuromuscular diseases⁴⁹ but is not known in aLOPD. As previously demonstrated⁵⁰, below a certain level of lower limb MMS, balance and risk of falling is strongly increased in aLOPD. Further studies are needed to investigate the relationship between lower limb MMS and balance in aLOPD. This would assist in determining a critical lower limb strength level below which balance is affected and risk of falling is strongly increased.

The standing posture of aLOPD is often characterized by a pelvic tilt with associated spinal deformities and could amplify stability problems². This specific organization could be related to pelvic and trunk stabilizer weakness. However, postural orientation has never been studied in LOPD. There is a need to quantify postural orientation using instrumented assessments such as 3D analysis systems. This would provide the organization of body segments of aLOPD in order to identify the resulting pathological compensations.

Strengths and limitations of this scoping review

This scoping review has some strengths and limitations that must be considered when interpreting the results. The research and analysis methodology applied has produced an exhaustive, clear and objective overview of current knowledge on the motor functions of aLOPD. However, most of the included studies are uncontrolled and have low levels of evidence. New RCTs and control case studies on large samples are essential to improve our knowledge of aLOPD motor function.

Conclusion

Here, we conducted a scoping review on motor functions in aLOPD. This research provides an overview of the current knowledge on evaluations, alterations and interventions concerning motor functions in aLOPD. It also underlines the lack of current research on motor functions. Complete instrumented explorations of neuromuscular performance and its associations with gait and postural control biomechanical assessments should be explored in future studies. This would i) provide a better understanding of the effect of LOPD on motor functions, ii) highlight new sensitive biomarkers for therapy trials, and iii) improve clinical management of aLOPD.

References

1. van der Ploeg AT, Reuser AJJ. Pompe's disease. *Lancet*. 2008;372(9646):1342-1353. doi:10.1016/S0140-6736(08)61555-X
2. Chan J, Desai AK, Kazi ZB, et al. The emerging phenotype of late-onset Pompe disease: A systematic literature review. *Mol Genet Metab*. 2017;120(3):163-172. doi:10.1016/j.ymgme.2016.12.004
3. van der Beek NAME, de Vries JM, Hagemans MLC, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis*. 2012;7:88. doi:10.1186/1750-1172-7-88
4. Laforêt P, Laloui K, Granger B, et al. The French Pompe registry. Baseline characteristics of a cohort of 126 patients with adult Pompe disease. *Rev Neurol (Paris)*. 2013;169(8-9):595-602. doi:10.1016/j.neurol.2013.07.002
5. Hagemans MLC, Winkel LPF, Van Doorn PA, et al. Clinical manifestation and natural course of late-onset Pompe's disease in 54 Dutch patients. *Brain*. 2005;128(3):671-677. doi:10.1093/brain/awh384
6. Massion J. Postural control system. *Curr Opin Neurobiol*. 1994;4(6):877-887. doi:10.1016/0959-4388(94)90137-6
7. Van Der Ploeg A.T., Clemens P.R., Corzo D., et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *New Engl J Med*. 2010;362(15):1396-1406. doi:10.1056/NEJMoa0909859
8. Semplicini C, De Antonio M, Taouagh N, et al. Long-term benefit of enzyme replacement therapy with alglucosidase alfa in adults with Pompe disease: Prospective analysis from the French Pompe Registry. *J Inherit Metab Dis*. Published online June 9, 2020. doi:10.1002/jimd.12272
9. Van Den Berg L.E.M., Favejee M.M., Wens S.C.A., et al. Safety and efficacy of exercise training in adults with Pompe disease: Evaluation of endurance, muscle strength and core stability before and after a 12 week training program. *Orphanet J Rare Dis*. 2015;10(1). doi:10.1186/s13023-015-0303-0
10. Sarah B, Giovanna B, Emanuela K, Nadi N, Josè V, Alberto P. Clinical efficacy of the enzyme replacement therapy in patients with late-onset Pompe disease: a systematic review and a meta-analysis. *J Neurol*. Published online April 13, 2021. doi:10.1007/s00415-021-10526-5
11. Peters MDJ, Marnie C, Tricco AC, et al. Updated methodological guidance for the conduct of scoping reviews. *JBIM Evid Synth*. 2020;18(10):2119-2126. doi:10.11124/JBIES-20-00167
12. Van der Beek N a. ME, Hagemans MLC, Reuser AJJ, et al. Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. *Neuromuscul Disord*. 2009;19(2):113-117. doi:10.1016/j.nmd.2008.11.007
13. Van der Ploeg A.T., Barohn R., Carlson L., et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. *Mol Genet Metab*. 2012;107(3):456-461. doi:10.1016/j.ymgme.2012.09.015
14. Harlaar L., Hogrel J.-Y., Perniconi B., et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology*. 2019;93(19):e1756-e1767. doi:10.1212/WNL.0000000000008441

15. Wokke JHJ, Escolar DM, Pestronk A, et al. Clinical features of late-onset Pompe disease: a prospective cohort study. *Muscle Nerve*. 2008;38(4):1236-1245. doi:10.1002/mus.21025
16. Figueroa-Bonaparte S, Segovia S, Llauger J, et al. Muscle MRI Findings in Childhood/Adult Onset Pompe Disease Correlate with Muscle Function. *PLoS ONE*. 2016;11(10):e0163493. doi:10.1371/journal.pone.0163493
17. Andreassen CS, Schlütter JM, Vissing J, Andersen H. Effect of enzyme replacement therapy on isokinetic strength for all major muscle groups in four patients with Pompe disease-a long-term follow-up. *Mol Genet Metab*. 2014;112(1):40-43. doi:10.1016/j.ymgme.2014.02.015
18. Alonso-Pérez J., Segovia S., Domínguez-González C., et al. Spanish Pompe registry: Baseline characteristics of first 49 patients with adult onset of Pompe disease. *Med Clin*. 2020;154(3):80-85. doi:10.1016/j.medcli.2019.03.036
19. Lollert A, Stihl C, Hötter AM, et al. Quantification of intramuscular fat in patients with late-onset Pompe disease by conventional magnetic resonance imaging for the long-term follow-up of enzyme replacement therapy. *PLoS ONE*. 2018;13(1):e0190784. doi:10.1371/journal.pone.0190784
20. van der Ploeg A, Carlier PG, Carlier RY, et al. Prospective exploratory muscle biopsy, imaging, and functional assessment in patients with late-onset Pompe disease treated with alglucosidase alfa: The EMBASSY Study. *Mol Genet Metab*. 2016;119(1-2):115-123. doi:10.1016/j.ymgme.2016.05.013
21. Pena L.D.M., Barohn R.J., Byrne B.J., et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. *Neuromuscular Disord*. 2019;29(3):167-186. doi:10.1016/j.nmd.2018.12.004
22. Terzis G., Dimopoulos F., Papadimas G.K., et al. Effect of aerobic and resistance exercise training on late-onset Pompe disease patients receiving enzyme replacement therapy. *Mol Genet Metab*. 2011;104(3):279-283. doi:10.1016/j.ymgme.2011.05.013
23. Sechi A, Zuccarelli L, Grassi B, et al. Exercise training alone or in combination with high-protein diet in patients with late onset Pompe disease: results of a cross over study. *Orphanet J Rare Dis*. 2020;15(1):143. doi:10.1186/s13023-020-01416-6
24. Bembi B., Pisa F.E., Confalonieri M., et al. Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. *J Inherit Metab Dis*. 2010;33(6):727-735. doi:10.1007/s10545-010-9201-8
25. Slonim A.E., Bulone L., Goldberg T., et al. Modification of the natural history of adult-onset acid maltase deficiency by nutrition and exercise therapy. *Muscle Nerve*. 2007;35(1):70-77. doi:10.1002/mus.20665
26. Favejee MM, van der Meijden JC, Kruijshaar ME, Rizopoulos D, van der Ploeg AT, Bussmann JBJ. Association of Muscle Strength and Walking Performance in Adult Patients With Pompe Disease. *Phys Ther*. 2018;98(11):925-931. doi:10.1093/ptj/pzy090
27. Angelini C, Semplicini C, Ravaglia S, et al. New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy. *Muscle Nerve*. 2012;45(6):831-834. doi:10.1002/mus.23340

28. McIntosh PT, Case LE, Chan JM, Austin SL, Kishnani P. Characterization of gait in late onset Pompe disease. *Molecular Genetics and Metabolism*. 2015;116(3):152-156. doi:10.1016/j.ymgme.2015.09.001
29. Schneider I, Zierz S, Schulze S, et al. Characterization of Gait and Postural Regulation in Late-Onset Pompe Disease. *Applied Sciences*. 2020;10(19):7001. doi:10.3390/app10197001
30. Starbuck C, Reay J, Silk E, Roberts M, Hendriksz C, Jones R. Are there common walking gait characteristics in patients diagnosed with late-onset Pompe disease? *Human Movement Science*. 2021;77:102777. doi:10.1016/j.humov.2021.102777
31. Stepien K.M., Hendriksz C.J., Roberts M., Sharma R. Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5 years. *Mol Genet Metab*. 2016;117(4):413-418. doi:10.1016/j.ymgme.2016.01.013
32. Strothotte S, Strigl-Pill N, Grunert B, et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. *J Neurol*. 2010;257(1):91-97. doi:10.1007/s00415-009-5275-3
33. Regnery C, Kornblum C, Hanisch F, et al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. *J Inherit Metab Dis*. 2012;35(5):837-845. doi:10.1007/s10545-012-9451-8
34. Figueroa-Bonaparte S, Llauger J, Segovia S, et al. Quantitative muscle MRI to follow up late onset Pompe patients: a prospective study. *Sci Rep*. 2018;8(1):10898. doi:10.1038/s41598-018-29170-7
35. Nuñez-Peralta C, Alonso-Pérez J, Llauger J, et al. Follow-up of late-onset Pompe disease patients with muscle magnetic resonance imaging reveals increase in fat replacement in skeletal muscles. *J Cachexia Sarcopenia Muscle*. Published online March 4, 2020. doi:10.1002/jcsm.12555
36. Koeberl D.D., Case L.E., Smith E.C., et al. Correction of Biochemical Abnormalities and Improved Muscle Function in a Phase I/II Clinical Trial of Clenbuterol in Pompe Disease. *Mol Ther*. 2018;26(9):2304-2314. doi:10.1016/j.ymthe.2018.06.023
37. Valle MS, Casabona A, Fiumara A, Castiglione D, Sorge G, Cioni M. Quantitative analysis of upright standing in adults with late-onset Pompe disease. *Sci Rep*. 2016;6:37040. doi:10.1038/srep37040
38. Tiffreau V, Ledoux I, Eymard B, Thévenon A, Hogrel JY. Isokinetic muscle testing for weak patients suffering from neuromuscular disorders: a reliability study. *Neuromuscul Disord*. 2007;17(7):524-531. doi:10.1016/j.nmd.2007.03.014
39. Maffiuletti NA, Aagaard P, Blazevich AJ, Folland J, Tillin N, Duchateau J. Rate of force development: physiological and methodological considerations. *Eur J Appl Physiol*. 2016;116(6):1091-1116. doi:10.1007/s00421-016-3346-6
40. Ravaglia S, Pichiecchio A, Ponzio M, et al. Changes in skeletal muscle qualities during enzyme replacement therapy in late-onset type II glycogenosis: temporal and spatial pattern of mass vs. strength response. *J Inherit Metab Dis*. 2010;33(6):737-745. doi:10.1007/s10545-010-9204-5
41. de Vries JM, Hagemans MLC, Bussmann JBJ, van der Ploeg AT, van Doorn PA. Fatigue in neuromuscular disorders: focus on Guillain-Barré syndrome and Pompe disease. *Cell Mol Life Sci*. 2010;67(5):701-713. doi:10.1007/s00018-009-0184-2
42. Place N, Millet GY. Quantification of Neuromuscular Fatigue: What Do We Do Wrong and Why? *Sports Med*. 2020;50(3):439-447. doi:10.1007/s40279-019-01203-9

43. Vanherpe P, Fieuws S, D'Hondt A, et al. Late-onset Pompe disease (LOPD) in Belgium: clinical characteristics and outcome measures. *Orphanet J Rare Dis*. 2020;15(1):83. doi:10.1186/s13023-020-01353-4
44. Schoser B, Stewart A, Kanter S, et al. Survival and long-term outcomes in late-onset Pompe disease following alglucosidase alfa treatment: a systematic review and meta-analysis. *J Neurol*. 2017;264(4):621-630. doi:10.1007/s00415-016-8219-8
45. Gidaro T, Gasnier E, Annonssamy M, et al. Home-based gait analysis as an exploratory endpoint during a multicenter phase 1 trial in limb girdle muscular dystrophy type R2 and facioscapulo-humeral muscular dystrophy. *Muscle & Nerve*. 2022;65(2):237-242. doi:10.1002/mus.27446
46. Khan A.A., Boggs T., Bowling M., et al. Whole-body magnetic resonance imaging in late-onset Pompe disease: Clinical utility and correlation with functional measures. *J Inherit Metab Dis*. 2020;43(3):549-557. doi:10.1002/jimd.12190
47. Cupler EJ, Berger KI, Leshner RT, et al. Consensus treatment recommendations for late-onset Pompe disease. *Muscle Nerve*. 2012;45(3):319-333. doi:10.1002/mus.22329
48. Ruhe A, Fejer R, Walker B. The test–retest reliability of centre of pressure measures in bipedal static task conditions – A systematic review of the literature. *Gait & Posture*. 2010;32(4):436-445. doi:10.1016/j.gaitpost.2010.09.012
49. Horlings CGC, Küng UM, van Engelen BGM, et al. Balance control in patients with distal versus proximal muscle weakness. *Neuroscience*. 2009;164(4):1876-1886. doi:10.1016/j.neuroscience.2009.09.063
50. Cattagni T, Scaglioni G, Laroche D, Van Hoecke J, Gremeaux V, Martin A. Ankle muscle strength discriminates fallers from non-fallers. *Front Aging Neurosci*. 2014;6. doi:10.3389/fnagi.2014.00336

Table 1: Methods of assessing motor functions in aLOPD

Measurement focus	Data collection method	References
Muscle strength	Manual muscle testing (MRC)	3,4,9,12,14,16,18,19,29,31–35,37,43,46
	Held hand dynameters	3,9,16,20,21,26,34,35,40
	Isokinetic dynamometer	17
	Isometric dynamometer	23
	Quantitative muscle test	7,13–15,22
Muscle function	Quick Motor Function Test	3,9,20,21
Locomotion biomechanics	Gait features analysis	28–30
Locomotion & ambulation (ability & performance test)	10 m walk test	9,15,16,20,21,27,29,32–36,43,46
	Climb 4-step test	8,9,15,16,19–21,27,32–36,46
	Timed Up and Go test	16,34,35
	GSGC	9,16,20,21,27,32–34,36,46
	WGM score	23–25,27–29,32,33,40
Postural control	Stability	40,48

GSGC: Gait, Stairs, Gower, Chair test; MRC : Medical Research Council

Figure 1: Prisma 2009 flow diagram

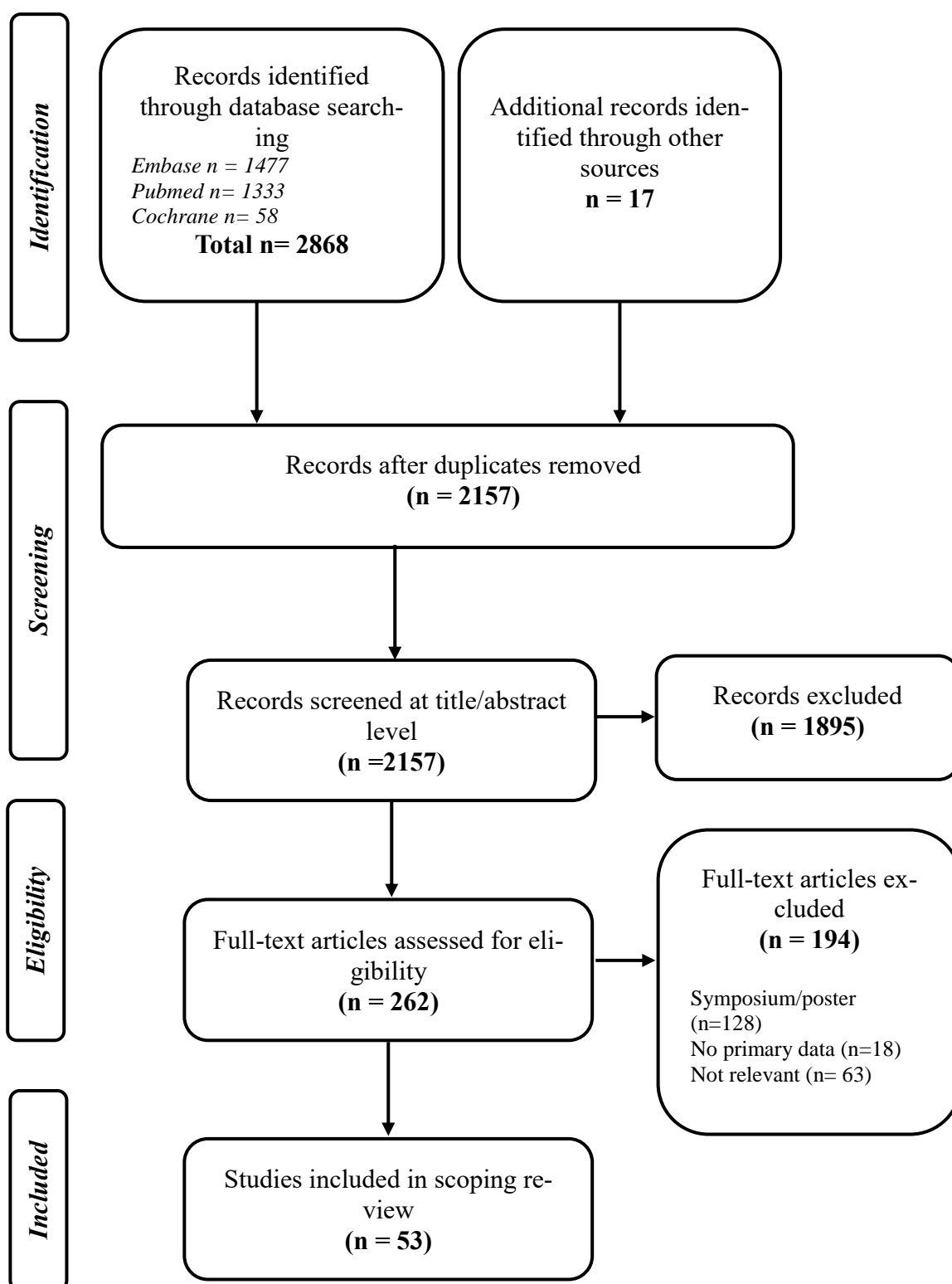


Figure 2: Risk of bias of included studies evaluated through the ROB.2 tool

		Risk of bias domains					
		D1	D2	D3	D4	D5	Overall
Study	Van der Ploeg 2010	-	+	+	+	+	-
	Koeberl 2018	-	+	+	+	-	-
	Koeberl 2020	-	+	+	+	-	-

Domains:

D1: Bias arising from the randomization process.
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement

-

Some concerns

+

Low

Figure 3: Risk of bias of included studies evaluated through the ROBIN-I tool

	Risk of bias domains							Overall
	D1	D2	D3	D4	D5	D6	D7	
Alandy-Dy (2019)	-	+	+	+	+	-	+	-
Anderson (2014)	-	+	+	+	-	-	+	-
Andreassen (2014)	-	+	+	+	+	+	-	-
Angelini (2009)	+	+	+	+	+	-	+	-
Angelini c. (2012)	-	-	+	+	+	+	+	-
Angelini (2012)	-	-	-	+	+	-	+	X
Bembi (2010)	-	+	+	+	+	-	+	-
De Vries (2012)	-	+	+	+	+	-	+	-
Fernández-Simón (2019)	-	+	+	+	+	-	+	-
Harlaar (2019)	+	+	+	+	+	-	+	-
Hundsberger T. (2014)	-	+	+	+	+	-	X	X
Koeberl D.D. (2014)	-	+	+	+	+	-	+	-
Kuperus (2017)	-	-	+	+	+	-	+	-
Pena L.D.M. (2019)	-	+	+	+	+	-	+	-
Ravaglia (2010)	-	+	+	+	+	-	+	-
Regnery (2012)	-	+	+	+	+	-	+	-
Ripolone (2018)	-	+	+	+	-	-	+	-
Scheidegger O. (2018)	-	+	+	+	+	-	+	-
Sechi A. (2020)	-	+	-	+	+	+	+	-
Semplicini (2020)	+	+	+	+	+	-	+	-
Slonim A.E. (2007)	-	+	+	+	-	-	+	-
Stepien K.M. (2016)	-	+	+	+	-	-	+	-
Strothotte (2010)	X	+	+	+	+	-	+	X
Terzis G. (2011)	-	+	+	+	+	-	+	-
Van Den Berg L.E.M. (2015)	-	+	+	+	+	+	+	-
Van der Ploeg (2012)	-	+	+	+	+	-	+	-
Van der Ploeg (2016)	-	+	+	+	+	-	+	-
Witkowski (2018)	X	+	+	+	+	-	+	X

Study

Domains:
D1: Bias due to confounding.
D2: Bias due to selection of participants.
D3: Bias in classification of interventions.
D4: Bias due to deviations from intended interventions.
D5: Bias due to missing data.
D6: Bias in measurement of outcomes.
D7: Bias in selection of the reported result.

Judgement
X Serious
- Moderate
+ Low

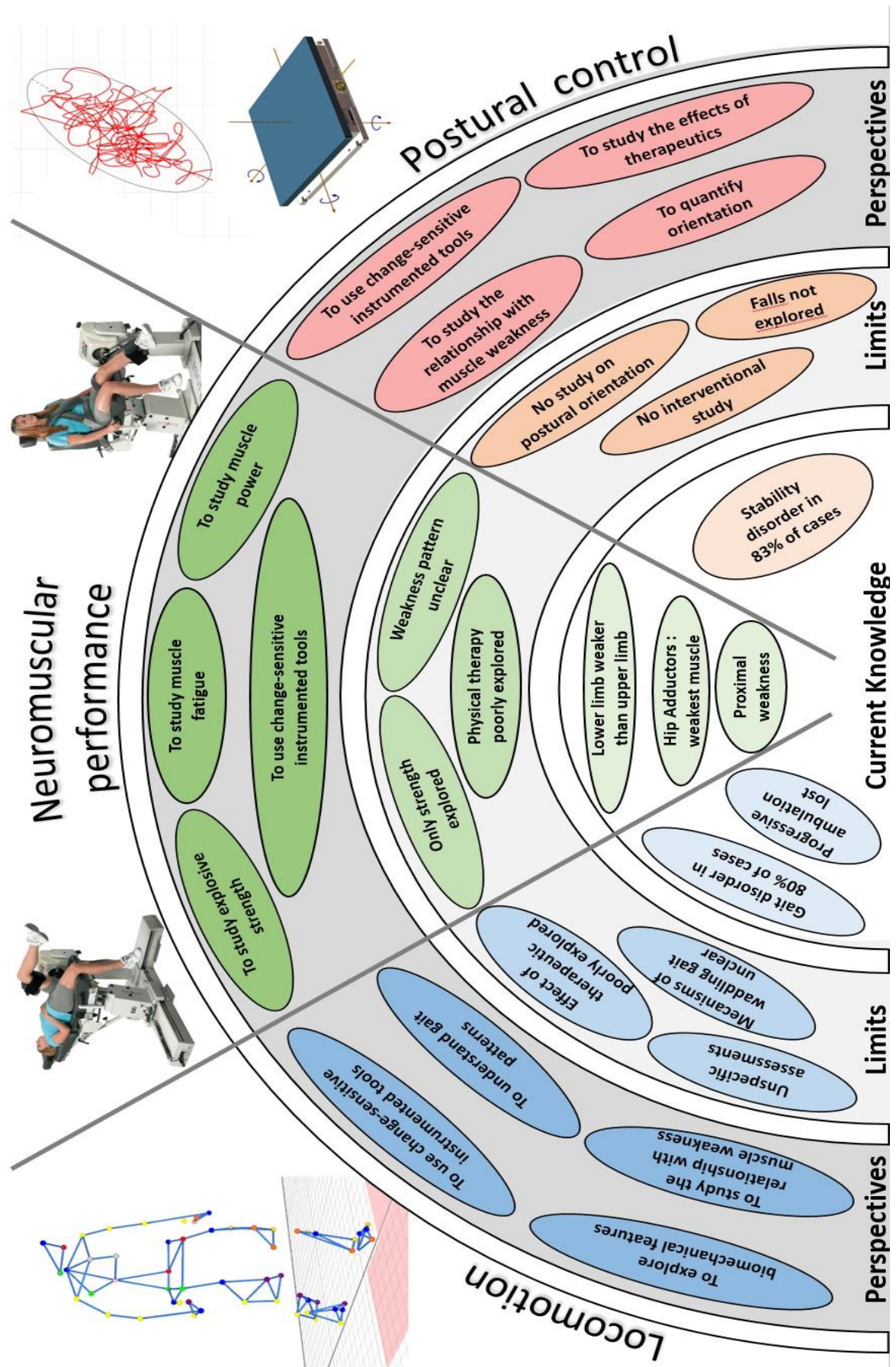
Figure 4: Risk of bias of included studies evaluated through the Newcastle-Ottawa Quality Assessment Scale

	Risk of bias			
	D1	D2	D3	Overall
Study	Figueroa-Bonaparte (2018)	+	+	+
	Filosto (2019)	+	+	-
	A. Khan (2020)	-	-	-
	Lollert (2018)	-	-	-
	Müller-Felber (2007)	-	-	-
	Nuñez-Peralta (2020)	+	+	-
	Pellegrini (2005)	X	-	-
	Van der Beek (2009)	-	-	+
	Van der Beek (2012)	+	+	+
	Vanherpe (2020)	-	-	-
	Wokke (2008)	-	-	-
	Valle (2016)	X	+	+
	Schneider (2020)	-	+	-
	Strabuck (2021)	+	+	+
	Fernández-Simón (2019)	+	+	+
	Rehmann (2020)	-	-	+

D1: Selection
 D2: Comparability
 D3: Outcome/Exposure

Judgement
 X High
 - Unclear
 + Low

Figure 5: Current knowledge, limits and perspective of motor function characteristics in late-onset Pompe disease



Supplemental content

A. eTable:

- eTable 1 Summary of data extraction by topic
- eTable 2 Additional reference for methods of assessing motor functions in adults with LOPD
- eTable 3 Muscle groups targeted in maximal muscle strength assessments

B. eMethod:

- eMethod Complement to the research methodology

C. eAppendix:

- eAppendix 1 Checklist PRISMA-ScR
- eAppendix 2 Complete list of articles included by topic

eTable 1: Summary of data extraction by topic

	Authors	Design	Sample (Mean WGM)	Purpose	Measures	Study findings
◆	De Jager et al. 1998	Cross sectional case series studies.	9 Un-treated (NA)	To observe muscle alteration by CT scans	M.S.T. CT scan	Specific alterations in lumbar paraspinal muscles, psoas, hamstrings, adductor. Positive correlation between CT score and MRC score.
◆	De Vries et al. 2012	NRSI	69 treated (NA)	To determine the Pompe disease's course with ERT	M.S.T. P.F.T.	Estimated disease duration: 20 years Increase in muscle strength (more with HHD). Follow-up: 23 months
◆	Pichiechio et al. 2004	Cross sectional case series studies.	11 Un-treated (NA)	To evaluate trunk and leg muscle alteration on MRI.	M.S.T. P.F.T. MRI	Estimated disease duration: 13 years Fatigue and, selective and symmetrical weakness reported. Paraspinal muscles, adductor magnus and semimembranosus were the first damaged on MRI. Correlation between strength and alterations was found on MRI.
◆	Van der Beek et al. 2009	Cohort study	16 Un-treated (NA)	To assess evolution of pulmonary function and muscle strength	M.S.T. P.F.T.	Estimated disease duration: 18.1 years Degradation of muscle strength of 0.5 points per year. 50% of patients lost ambulation. Authors criticized the MRC.
◆	Van der Beek et al. 2012	Cohort study	94 Un-treated (NA)	To study the natural disease course.	M.S.T. P.F.T.	Estimated disease duration: 15.3 years Symmetrical weakness influenced by age of onset disease and pulmonary impairments. 80% had, trunk muscles hip muscles and shoulder abductor weakness. Trunk muscles were affected during the early stage of the disease. Strength loss of -1.3 points per year (MMT) and -2.6% per year (HHD).
◆	Vanden Berg et al. 2010	Control case	36 Treated (NA)	To assess the bone mineral	M.S.T. Bone density P.F.T.	Estimated disease duration: 15 years 26% of patients had osteoporosis. Bone density correlated with total body muscle strength.
◆ ●	Anderson et al. 2014	NRSI	62 treated (NA)	To determine the effectiveness of ERT	6- MWT M.S.T. P.F.T.	Estimated disease duration: 7 years 6-MWT and muscle strength improved in the first two years after starting ERT, then declined.
◆ ●	Andreassen et al. 2014	NRSI	4 treated (3)	To follow patients treated with ERT.	6- MWT M.S.T. P.F.T.	Strength improved during the first years, then decreased or stagnated. Dynamometer relevant for follow-up.
◆ ●	Angelini et al. 2009	NRSI	11 treated (3.1)	To follow up clinical response of ERT	6- MWT G.A.P.T. M.S.T. P.F.T.	Estimated disease duration: 13 years Case series, not statistics, 6-MWT muscle strength tends to improve slightly with ERT.
◆ ●	Favejee et al. 2018	Cross sectional case series studies.	107 treated (NA)	To determine relations between gait and strength.	G.A.P.T. M.S.T.	Estimated disease duration: 15 years Only 18% of aLOPD had a normal gait. Walking performance decreased with age, gender and hip flexor and abductor muscle weakness.
◆ ●	Fernández-Simón et al. 2019	Control case	37 LOPD 23 treated 45 control (NA)	To study muscle degeneration in people with LOPD.	6- MWT G.A.P.T. M.S.T. MRI	Estimated disease duration: 17 years No significant correlation between serum PDGF-BB concentration and muscle strength or 6- MWT.
◆ ●	Fernández-Simón et al. 2019	NRSI	25 Treated (NA)	To describe production and impact of antibodies in LOPD patients.	6- MWT G.A.P.T. M.S.T. MRI	Estimated disease duration: 15 years 72% of patients had antibodies. No difference between seropositive and seronegative patients for clinical outcomes.
◆ ●	Figueroa-Bonaparte et al. 2016	Cross sectional case series studies.	34 LOPD 23 treated (NA)	To compare muscle function tests with MRI assessment	6- MWT G.A.P.T. M.S.T. MRI	Estimated disease duration: 15 years Hip adductor, extensors and flexors are altered on MRI. Strong correlation between muscle strength, 6-MWT and fatty replacement in muscle MRI
◆ ●	Figueroa-Bonaparte et al. 2018	Cohort study.	32 LOPD 22 Treated (NA)	To compare the change in MRI and clinical outcomes.	6- MWT G.A.P.T. M.S.T. MRI P.F.T.	Estimated disease duration: 17 years No significant change in clinical tests and 1.7% increase in fat fraction in patients treated after 1 year. Fat fraction more sensitive than motor tests for disease progression.
◆ ●	Filosto et al. 2019	Cohort study	64 Treated (NA)	To study production and impact of GAA antibodies in LOPD.	6- MWT G.A.P.T. M.S.T. P.F.T.	Significant improvement in strength only in seronegative patients. The improvement was greater in the first 36 months of treatment. No change in other outcomes

◆ ●	Harfouche et al. 2020	Cross sectional case series studies.	30 Treated (NA)	To study validity of questionnaires and clinical tests.	6- MWT M.S.T. P.F.T.	Estimated disease duration: 20 years Significant correlation between 6-MWT and arm function, overall strength and arm function.
◆ ●	Harlaar et al. 2019	NRSI	30 Treated (NA)	To determine effects of 10 years of ERT in LOPD.	6- MWT M.S.T. P.F.T.	Estimated disease duration: 17 years Strength and lung capacity improved during the first 3 years, then declined, 6-MWT lower after 10 years than the baseline. Positive impact of ERT in 93% of patients for 3 to 5 years.
◆ ●	Hundsberger et al. 2014	NRSI	7 Treated (NA)	To monitor the ERT cessation in LOPD patients.	6- MWT M.S.T. P.F.T.	After discontinuation of treatment 6-MWT and MRC decreased. Resumption of treatment induced only partial recovery.
◆ ●	Illes et al. 2014	Cross sectional case series studies.	7 Treated (NA)	To examine motor function.	6- MWT M.S.T. G.A.P.T. P.F.T.	Estimated disease duration: 15.6 years. The ratio of hamstring-quadriceps strength was lower in aLOPD than in healthy individuals. The thigh strength is correlated to the time to climb 4 steps.
◆ ●	Khan et al. 2020	Cohort study	19 LOPD 16 Treated (NA)	To correlate muscle strength clinical outcomes and fat fractions.	M.S.T. G.A.P.T. MRI	The fat inclusion was major in the lumbar extensors, hip adductors and gluteus medius. Muscle strength correlated with infiltration and GSGC. No change in infiltration at 2 years.
◆ ●	Koeberl et al. 2020	RCT.	12 Treated (NA)	To determine effects of albuterol + ERT.	6- MWT M.S.T. G.A.P.T. P.F.T.	Significant increase in lung function, 6- MWT, and functional scores after 24 weeks and only for the albuterol + ERT group.
◆ ●	Koeberl et al. 2018	RCT.	12 Treated (NA)	To determine muscular effects of Clenbuterol with ERT therapy.	6- MWT M.S.T. G.A.P.T. P.F.T.	Increase in 6- MWT, GSGC, QMFT at 52 weeks only for the clenbuterol + ERT group.
◆ ●	Koeberl et al. 2014	NRSI	7 Treated (NA)	To evaluate effects of adjunctive albuterol to ERT	6- MWT M.S.T.	6- MWT increased with albuterol adjunction and strength increased in all patients.
◆ ●	Kuperus et al. 2017	NRSI	102 Treated (NA)	To determine the effect of ERT and identify predictors of a favorable response.	6- MWT M.S.T. P.F.T.	Estimated disease duration: 16 years Treated patients had better progression of muscle strength and 6-MWT than the natural history. Improvements were during the first 2-3 years of treatment.
◆ ●	Laforet et al. 2000	Cross sectional case series studies.	18 Untreated (4)	To characterize phenotypes of LOPD patients	M.S.T. G.A.P.T. CT scan P.F.T.	Estimated disease duration: 13 years 75% of patients had walking or running difficulties. Weakness is symmetric and selective.
◆ ●	Laforet et al. 2013	Cross sectional case series studies.	126 LOPD (NA)	To characterize the phenotypes of LOPD in French	6- MWT M.S.T. Questionary	Patients had limitations when getting up from a squatting position (89%), getting up from a chair (83%), climbing stairs (90%), standing/supine transfer (90%). Assistive device was needed in 45% of patients.
◆ ●	Lollert et al. 2018	Cohort study	41 Treated (NA)	To compare MRI to clinical parameters.	6- MWT M.S.T. G.A.P.T. MRI P.F.T.	Interobserver agreement was good for mercuri and very good for fat fractions. Correlations between MRI score 6-MWT and MRC score. Decrease in 4-step stair climbing time and 6-MWT distance.
◆ ●	Núñez-Peralta et al. 2020 Spain	Cohort study	36 LOPD 23 treated (NA)	To describe the changes observed in fat replacement for 4 years.	M.S.T. G.A.P.T. MRI P.F.T.	Estimated disease duration: 9.4 years The hip and knee muscle strength decreased and fat fraction increase of 1.9% per year. Age at the ERT initiation and fat inclusion were correlated.
◆ ●	Pellegrini et al. 2005	Cohort study.	29 Un-treated (4.2)	To evaluate the link between gait and respiratory.	M.S.T. G.A.P.T. P.F.T.	The decrease of VC was correlated with MMT.
◆ ●	Pena et al. 2019	NRSI	24 LOPD 14 Treated (NA)	To evaluate the safety and efficacy of avalglucosidase alfa, .	6- MWT M.S.T. G.A.P.T. P.F.T.	Test results were stable with no correlation with groups or dose levels.
◆ ●	Ravaglia et al. 2010	NRSI	11 Treated (3)	To study changes in muscle mass and quality	6- MWT M.S.T. G.A.P.T. MRI P.F.T.	Estimated disease duration: 26 years. Weakness was greater in the adductors and hamstrings than in distal muscles. Fat inclusions were found in the posterior thigh. After treatment, the knee strength and 6-MWT increased.

◆ ●	Regnery et al. 2012 Germany	NRSI	38 Treated (4.45)	To follow the evolution of aLOPD treated	6- MWT M.S.T. G.A.P.T. P.F.T.	Estimated disease duration: 14.5 years Increase in 6-MWT at 12 months but not at 24 months. No change in other outcomes. Some intra-individual and inter-individual variations reported.
◆ ●	Rehmann et al. 2020	Control case	18 LOPD 14 treated 30 controls (NA)	To assess MRI differences in diffusion metrics in patients' leg muscles.	6- MWT M.S.T. MRI	Fat fraction was significantly higher in the calf and thigh muscle in LOPD than in controls. Structural damage, scar tissue, fatty infiltration of the leg muscle found.
◆ ●	Scheidegger et al. 2018	NRSI	7 Treated (NA)	To monitor the ERT resumption in LOPD patients.	6- MWT M.S.T. G.A.P.T. P.F.T.	Long-term discontinuation of ERT resulted in deterioration of clinically significant parameters and quality of life.
◆ ●	Sechi et al. 2020	NRSI	13 Treated (3)	To evaluate the effects of physical training alone or with a protein diet in treated patients.	6- MWT M.S.T. G.A.P.T. P.F.T.	Estimated disease duration: 8 years Improvement of aerobic peak in both groups, but more in the diet group and decreased after washout.
◆ ●	Slonim et al. 2007	NRSI	34 Un-treated (3.2)	To evaluate the effects of physical training with diet in treated patients for 10 years.	M.S.T. G.A.P.T. P.F.T.	Walton's score deteriorations was slower in the 26 highly compliant patients. Greatest improvement in muscle function, for compliant group.
◆ ●	Stepien et al. 2016	NRSI	22 Treated (NA)	To assess the impact of ERT on mobility	6- MWT M.S.T. P.F.T.	Estimated disease duration: 11.5 years Walking aids required for 55% of patients. 10-15 years after diagnosis of LOPD, 30-50% of patients lost ambulation.
◆ ●	Strothotte et al. 2010	NRSI	44 Treated (NA)	To determine the effectiveness of ERT.	6- MWT M.S.T. G.A.P.T. P.F.T.	Stabilization after 1 year, with a very high variability between participants.
◆ ●	Terzi et al. 2011 Greece	NRSI	5 Treated (NA)	To study effects training programs on strength and gait.	6- MWT M.S.T.	Muscle strength and walking distance improved after training.
◆ ●	Van den Berg et al. 2015	NRSI	23 Treated (NA)	To compare effects of training programs added to ERT with ERT alone.	6- MWT M.S.T. G.A.P.T. P.F.T.	Estimated disease duration: 15.8 years No change after 12 weeks of ERT alone. Balance, stairs climbing and hip flexors and shoulder adductor strength and 6-MWT improved after 12 weeks of training. Authors recommended the use of 6- MWT for assessing endurance.
◆ ●	Van der Ploeg et al. 2012	NRSI	81 Treated (NA)	To determine the efficacy and safety of ERT	6- MWT M.S.T. P.F.T.	General stabilization. Most strongly improvements in the early years of the ERT. 6- MWT was dependent on the patient's motivation.
◆ ●	Van der Ploeg et al. 2010	RCT.	90 LOPD 60 treated (NA)	To assess the impact of ERT on motor functions	6- MWT M.S.T. P.F.T.	Estimated disease duration: 9.3 years Baseline 6-MWT: 52% of predicted distance. Improvement of 6-MWT in ERT group No change in muscle strength. Greatest improvements in the treated group occurred in the first 26 weeks.
◆ ●	Van der Ploeg et al. 2016	NRSI	16 Treated (NA)	To characterize functional effects of ERT for 6 months.	6- MWT M.S.T. P.F.T. MRI	Estimated disease duration: 14.4 years Fat infiltration of quadriceps and deltoid decreased. 6- MWT and QMFT improved after 6 months of ERT.
◆ ●	Vanherpe et al. 2020	Cohort study	52 treated (NA)	To study the clinical, genetic and brain imaging in LOPD.	6- MWT M.S.T. G.A.P.T. P.F.T.	Initial symptoms were limb-girdle weakness. After initial improvements, 6-MWT and strength declined.
◆ ●	Wokke et al. 2008	Cohort study	58 Un-treated (NA)	To characterize clinical presentation and disease progression of LOPD	6- MWT M.S.T. P.F.T.	Estimated disease duration: 14.7 years 6-MWT: 53.7% of predicted distance. Over 1 year, degradation of lower limb muscles strength was greater than upper limb muscles (7% vs. 4%). Time since symptom onset weakness.

◆ ●	Yuan et al. 2020	Cross sectional case series studies.	121 Treated (NA)	To study the links between physical outcomes and PROMs in cross-section.	6- MWT M.S.T. P.F.T.	Estimated disease duration: 16 years 6-MWT: 53.7% of predicted distance. Participation, daily-life activities and the physical component of quality of life were positively correlated with muscle strength, FVC and 6- MWT.
●	Alandy-dy et al. 2019	NRSI	18 Treated (NA)	To follow patients treated with ERT	6- MWT P.F.T	Estimated disease duration: 25 years 6MWT was declining by 11.6 m per year
●	Angelini et al. 2012	NRSI	40 treated (3.1)	To study the GSGC and follow patients treated.	6- MWT G.A.P.T. P.F.T.	Estimated disease duration: 15 years. GSGC correlated with walking performance. Significant decrease in performance after 12 months of ERT.
●	Angelini et al. 2012	NRSI	74 treated (NA)	To determine motor effects of 4 years of ERT	6- MWT G.A.P.T. P.F.T.	Estimated disease duration: 14.7 years. Increase of 6MWT and no change in WGMS after ERT
●	Bembi et al. 2010	NRSI	17 Treated (5)	To evaluate the ERT long-term effects.	6- MWT G.A.P.T. P.F.T.	Estimated disease duration: 20 years. ERT improved 6- MWT (independently of impairment/age). ERT improved WGMS (patients with moderate impairment).
●	McIntosh et al. 2015	Cross sectional case series studies.	22 Treated (NA)	Characterization of Gait parameters in LOPD	6- MWT Gait parameter	Walking speed and stride length were lower and double support time was increasing in aLOPD compared to norms. The 6MWT is insufficient. 3D analysis recommended by authors.
●	Müller-Felber et al. 2007	Cohort study	32 Untreated (2.3)	To describe clinical and radiological outcomes	M.S.T. G.A.P.T. MRI P.F.T.	Estimated disease duration: 10 years. Mean time between onset and diagnosis was 10.4 years. The first symptom was limb-girdle muscle weakness. Ambulation lost was observed in 33%.
●	Riplonne et al. 2018	NRSI	18 treated (NA)	To determine influence of ERT on skeletal muscle	6- MWT P.F.T.	Estimated disease duration: 14.5 years No change for 6-MWT after 6 months.
●	Starbuck et al. 2021	Control case	12 Un-treated 12 controls (NA)	To compare gait parameters of aLOPD with controls.	6- MWT Gait parameters	Thoracic sway, sagittal pelvic and maximal hip adduction range of motion increased in patients. Lower hip and knee extension moments and maximal hip generation powers in LOPDs. High phenotype's variability. 6-MWT: $68.7 \pm 14.1\%$ of predicted distance.
●	Semplicini et al. 2020	NRSI	197 LOPD 158 Treated (NA)	To observe long-term effect of ERT on clinical assessments	6- MWT G.A.P.T. P.F.T.	Estimated disease duration: 14.9 years Initial increase (2.2 years) of 6MWT, then progressive decline. Smaller improvement in patients with the greatest lung impairments.
●	Witkowski et al. 2018	NRSI	5 treated (NA)	To study 6-year follow-up patients with ERT.	6- MWT P.F.T.	6MWT increased in the first three then decline
◆ ● ●	Schneider et al. 2020	Control case	16 LOPD 15 treated (NA)	To evaluate gait parameters and postural abilities	6- MWT M.S.T. G.A.P.T Stability	Estimated disease duration: 15.9 years Stability and postural regulation reduced in patients. Reduced gait speed, and stride length and, increased double stance time in patients.
◆ ● ●	Valle et al. 2016	Control case	5 Treated 5 controls (NA)	To compare LOPD/healthy postural stability.	M.S.T. Stability indicator	Stability reduced compared to healthy participants. Stability decreased, especially in the anteroposterior direction and eyes closed.

NRSI: Non-randomized studies of interventions; RCT: Randomized Control Trial;

NA: Not available

M.S.T.: Muscle strength tests; P.F.T.: Pulmonary Function Tests; G.A.P.T: Gait ability and Performance Tests

ERT: Enzyme Replacement therapy; WGMS: Walton Gardner Medwin Score; HHD: Held Hand Dynameter

GSGC: Gait, Stairs, Gower, Chair test; QMFT: Quick Motor Function Test; MRC: Medical Research Council

◆ **Neuromuscular focus**

● **Locomotion focus**

● **Postural control focus**

eTable 2: Additional reference for methods of assessing motor functions in adults with LOPD

Measurement focus	Data collection method	Additional References
Muscle strength	Manual muscle testing (MRC)	1–15
	Held hand dynameters	2,3,6,8,10,16,17
	Isokinetic dynamometer	18
	Isometric dynamometer	-
	Quantitative muscle test	-
Muscle function	Quick Motor Function Test	2,6
Locomotion biomechanics	Gait features analysis	-
Locomotion (ability & performance test)	10 m walk test	3,4,7,10,19
	Climb 4-step test	3,4,10,17,18
	Timed Up and Go test	3,10
	GSGC	3,4,10,19
	Walton Gardner Medwin score	13
Postural control	Stability	-

GSGC: Gait, Stairs, Gower, Chair test; MRC: Medical Research Council

References:

1. Anderson L.J., Henley W., Wyatt K.M., et al. Effectiveness of enzyme replacement therapy in adults with late-onset Pompe disease: results from the NCS-LSD cohort study. *J Inherit Metab Dis.* 2014; 37(6):945-952. doi:10.1007/s10545-014-9728-1
2. De Vries J.M., Van Der Beek N.A., Hop W.C., et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: An open-label single-center study. *Orphanet J Rare Dis.* 2012; 7(1). doi:10.1186/1750-1172-7-73
3. Fernandez-Simon E, Carrasco-Rozas A, Gallardo E, et al. PDGF-BB serum levels are decreased in adult onset Pompe patients. *Sci Rep.* 2019; 9(1):2139. doi:10.1038/s41598-018-38025-0
4. Filosto M, Cotti Piccinelli S, Ravaglia S, et al. Assessing the Role of Anti rh-GAA in Modulating Response to ERT in a Late-Onset Pompe Disease Cohort from the Italian GSDII Study Group. *Adv Ther.* 2019; 36(5):1177-1189. doi:10.1007/s12325-019-00926-5
5. Hundsberger T., Rösler K.M., Findling O. Cessation and resuming of alglucosidase alfa in Pompe disease: a retrospective analysis. *J Neurol.* 2014; 261(9):1684-1690. doi:10.1007/s00415-014-7402-z
6. Kuperus E., Kruijschaar M.E., Wens S.C.A., et al. Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study. *Neurology.* 2017; 89(23):2365-2373. doi:10.1212/WNL.0000000000004711
7. Scheidegger O., Leupold D., Sauter R., Findling O., Rösler K.M., Hundsberger T. 36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry. *J Neurol.* 2018; 265(12):2783-2788. doi:10.1007/s00415-018-9065-7
8. Yuan M, Andrinopoulou ER, Kruijschaar ME, et al. Positive association between physical outcomes and patient-reported outcomes in late-onset Pompe disease: a cross sectional study. *Orphanet J Rare Dis.* 2020; 15(1):232. doi:10.1186/s13023-020-01469-7

9. De Jager A.E.J., Van Der Vliet T.M., Van Der Ree T.C., Oosterink B.J., Loonen M.C.B. Muscle computed tomography in adult-onset acid maltase deficiency. *Muscle Nerve*. 1998; 21(3):398-400. doi:10.1002/(SICI)1097-4598(199803)21:3<398::AID-MUS15>3.0.CO;2-W
10. Fernández-Simón E., Carrasco-Rozas A., Gallardo E., et al. Study of the effect of anti-rhGAA antibodies at low and intermediate titers in late onset Pompe patients treated with ERT. *Mol Genet Metab*. 2019; 128(1-2):129-136. doi:10.1016/j.ymgme.2019.07.013
11. Harfouche M, Kishnani PS, Krusinska E, et al. Use of the patient-reported outcomes measurement information system (PROMIS®) to assess late-onset Pompe disease severity. *J Patient Rep Outcomes*. 2020; 4(1):83. doi:10.1186/s41687-020-00245-2
12. Laforêt P., Nicolino M., Eymard B., et al. Juvenile and adult-onset acid maltase deficiency in France: Genotype-phenotype correlation. *Neurology*. 2000; 55(8):1122-1128. doi:10.1212/WNL.55.8.1122
13. Müller-Felber W, Horvath R, Gempel K, et al. Late onset Pompe disease: Clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. *Neuromuscular Disorders*. 2007; 17(9):698-706. doi:10.1016/j.nmd.2007.06.002
14. Pellegrini N., Laforet P., Orlikowski D., et al. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. *Eur Respir J*. 2005; 26(6):1024-1031. doi:10.1183/09031936.05.00020005
15. Pichiecchio A., Uggetti C., Ravaglia S., et al. Muscle MRI in adult-onset acid maltase deficiency. *Neuromuscular Disord*. 2004; 14(1):51-55. doi:10.1016/j.nmd.2003.08.003
16. van den Berg L.E.M., Zandbergen A.A., van Capelle C.I., et al. Low bone mass in Pompe disease. Muscular strength as a predictor of bone mineral density. *Bone*. 2010; 47(3):643-649. doi:10.1016/j.bone.2010.06.021
17. Koeberl D.D., Austin S., Case L.E., et al. Adjunctive albuterol enhances the response to enzyme replacement therapy in late-onset Pompe disease. *FASEB J*. 2014; 28(5):2171-2176. doi:10.1096/fj.13-241893
18. Illes Z, Mike A, Trauninger A, Vardi K, Vaczi M. Motor function and respiratory capacity in patients with late-onset pompe disease. *Muscle Nerve*. 2014; 49(4):603-606. doi:10.1002/mus.24142
19. Koeberl DD, Case LE, Desai A, et al. Improved muscle function in a phase I/II clinical trial of albuterol in Pompe disease. *Mol Genet Metab*. 2020; 129(2):67-72. doi:10.1016/j.ymgme.2019.12.008

eTable 3: Muscle groups targeted in maximal muscle strength assessments

Joins	Muscles	n	references
<i>Lower limb 41/48 studies</i>			
Hip	Hip flexors	28/48	1–28
	Hip extensors	21/48	1,4–8,10,12–19,21,23,25,26,28,29
	Hip adductors	14/48	4,5,7,8,10,13,18,19,21,23,26,28,30,31
	Hip abductors	15/48	3–5,7,8,10,11,13,18,19,21,23,26–28
Knee	Knee flexors	30/48	1–8,10,12–19,21–23,25–28,30–35
	Knee extensors	34/48	1–8,10–35
Ankle	Dorsiflexors	16/48	1,2,4,5,8,12–18,24,25,27,30
	Plantar flexors	14/48	1,2,4,5,12–16,18,24,27,30
<i>Upper limb 31/48 studies</i>			
Shoulder	Shoulder adductors	10/48	1,2,10,19,21,23,26,31,33,34
	Shoulder abductors	17/48	1,4,5,7,10,14,17,19–28
Elbow	Elbow flexors	25/48	1,2,4–7,10,12,14,17,19–29,31–34
	Elbow extensors	22/48	1,2,4–7,10,12,14,17,19,21–23,25–28,31–34
<i>Trunk muscle 15/48</i>			
Trunk	Paraspinal	4/48	4,5,9,13
	Neck	13/48	4,5,7,10,14,19,21,23,25–28

References

- Andreassen C.S., Schlütter J.M., Vissing J., Andersen H. Effect of enzyme replacement therapy on isokinetic strength for all major muscle groups in four patients with Pompe disease-a long-term follow-up. *Mol Genet Metab.* 2014; 112(1):40-43. doi:10.1016/j.ymgme.2014.02.015
- De Jager A.E.J., Van Der Vliet T.M., Van Der Ree T.C., Oosterink B.J., Loonen M.C.B. Muscle computed tomography in adult-onset acid maltase deficiency. *Muscle Nerve.* 1998; 21(3):398-400. doi:10.1002/(SICI)1097-4598(199803)21:3<398::AID-MUS15>3.0.CO;2-W
- Favejee MM, van der Meijden JC, Kruijshaar ME, Rizopoulos D, van der Ploeg AT, Bussmann JBJ. Association of Muscle Strength and Walking Performance in Adult Patients With Pompe Disease. *Phys Ther.* 2018; 98(11):925-931. doi:10.1093/ptj/pzy090
- Figuerola-Bonaparte S, Llauger J, Segovia S, et al. Quantitative muscle MRI to follow up late onset Pompe patients: a prospective study. *Sci Rep.* 2018; 8(1):10898. doi:10.1038/s41598-018-29170-7
- Figuerola-Bonaparte S, Segovia S, Llauger J, et al. Muscle MRI Findings in Childhood/Adult Onset Pompe Disease Correlate with Muscle Function. *PLoS One.* 2016; 11(10):e0163493. doi:10.1371/journal.pone.0163493
- Harfouche M, Kishnani PS, Krusinska E, et al. Use of the patient-reported outcomes measurement information system (PROMIS®) to assess late-onset Pompe disease severity. *J Patient Rep Outcomes.* 2020; 4(1):83. doi:10.1186/s41687-020-00245-2
- Harlaar L., Hogrel J.-Y., Perniconi B., et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology.* 2019; 93(19):e1756-e1767. doi:10.1212/WNL.0000000000008441

8. Khan A.A., Boggs T., Bowling M., et al. Whole-body magnetic resonance imaging in late-onset Pompe disease: Clinical utility and correlation with functional measures. *J Inherit Metab Dis.* 2020; 43(3):549-557. doi:10.1002/jimd.12190
9. Lollert A., Stihl C., Hötter A.M., et al. Quantification of intramuscular fat in patients with late-onset Pompe disease by conventional magnetic resonance imaging for the long-term follow-up of enzyme replacement therapy. *PLoS ONE.* 2018; 13(1). doi:10.1371/journal.pone.0190784
10. Nuñez-Peralta C., Alonso-Pérez J., Llauger J., et al. Follow-up of late-onset Pompe disease patients with muscle magnetic resonance imaging reveals increase in fat replacement in skeletal muscles. *J Cachexia Sarcopenia Muscle.* 2020;((Nuñez-Peralta C.; Llauger J.; Martínez-Noguera A.) Radiology Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain). doi:10.1002/jcsm.12555
11. Pellegrini N., Laforet P., Orlikowski D., et al. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. *Eur Respir J.* 2005; 26(6):1024-1031. doi:10.1183/09031936.05.00020005
12. Pena L.D.M., Barohn R.J., Byrne B.J., et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. *Neuromuscular Disord.* 2019; 29(3):167-186. doi:10.1016/j.nmd.2018.12.004
13. Pichiecchio A., Uggetti C., Ravaglia S., et al. Muscle MRI in adult-onset acid maltase deficiency. *Neuromuscular Disord.* 2004; 14(1):51-55. doi:10.1016/j.nmd.2003.08.003
14. Regnery C., Kornblum C., Hanisch F., et al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. *J Inherit Metab Dis.* 2012; 35(5):837-845. doi:10.1007/s10545-012-9451-8
15. Rehmann R., Froeling M., Rohm M., et al. Diffusion tensor imaging reveals changes in non-fat infiltrated muscles in late onset Pompe disease. *Muscle Nerve.* Published online 2020. doi:10.1002/mus.27021
16. Schneider I., Zierz S., Schulze S., et al. Characterization of Gait and Postural Regulation in Late-Onset Pompe Disease. *Applied Sciences.* 2020; 10(19):7001. doi:10.3390/app10197001
17. Strothotte S., Strigl-Pill N., Grunert B., et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2: 12-month results of an observational clinical trial. *J Neurol.* 2010; 257(1):91-97. doi:10.1007/s00415-009-5275-3
18. Valle M.S., Casabona A., Fiumara A., Castiglione D., Sorge G., Cioni M. Quantitative analysis of upright standing in adults with late-onset Pompe disease. *Sci Rep.* 2016; 6((Valle M.S.; Casabona A.; Cioni M.) Gait and Posture Analysis Laboratory, Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy):37040. doi:10.1038/srep37040
19. Van Den Berg L.E.M., Favejee M.M., Wens S.C.A., et al. Safety and efficacy of exercise training in adults with Pompe disease: Evaluation of endurance, muscle strength and core stability before and after a 12 week training program. *Orphanet J Rare Dis.* 2015; 10(1). doi:10.1186/s13023-015-0303-0
20. Van der Beek N.A.M.E., Hagemans M.L.C., Reuser A.J.J., et al. Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. *Neuromuscular Disord.* 2009; 19(2):113-117. doi:10.1016/j.nmd.2008.11.007
21. van der Beek NAME, de Vries JM, Hagemans MLC, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis.* 2012; 7:88. doi:10.1186/1750-1172-7-88
22. Vanherpe P., Fieuws S., D'Hondt A., et al. Late-onset Pompe disease (LOPD) in Belgium: Clinical characteristics and outcome measures. *Orphanet J Rare Dis.* 2020; 15(1). doi:10.1186/s13023-020-01353-4
23. De Vries J.M., Van Der Beek N.A., Hop W.C., et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: An open-label single-center study. *Orphanet J Rare Dis.* 2012; 7(1). doi:10.1186/1750-1172-7-73
24. Filosto M., Cotti Piccinelli S., Ravaglia S., et al. Assessing the Role of Anti rh-GAA in Modulating Response to ERT in a Late-Onset Pompe Disease Cohort from the Italian GSDII Study Group. *Adv Ther.* 2019; 36(5):1177-1189. doi:10.1007/s12325-019-00926-5

25. Hundsberger T., Rösler K.M., Findling O. Cessation and resuming of alglucosidase alfa in Pompe disease: a retrospective analysis. *J Neurol.* 2014; 261(9):1684-1690. doi:10.1007/s00415-014-7402-z
26. Kuperus E., Kruijshaar M.E., Wens S.C.A., et al. Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study. *Neurology.* 2017; 89(23):2365-2373. doi:10.1212/WNL.0000000000004711
27. van den Berg L.E.M., Zandbergen A.A., van Capelle C.I., et al. Low bone mass in Pompe disease. Muscular strength as a predictor of bone mineral density. *Bone.* 2010; 47(3):643-649. doi:10.1016/j.bone.2010.06.021
28. Yuan M, Andrinopoulou ER, Kruijshaar ME, et al. Positive association between physical outcomes and patient-reported outcomes in late-onset Pompe disease: a cross sectional study. *Orphanet J Rare Dis.* 2020; 15(1):232. doi:10.1186/s13023-020-01469-7
29. Terzis G., Dimopoulos F., Papadimas G.K., et al. Effect of aerobic and resistance exercise training on late-onset Pompe disease patients receiving enzyme replacement therapy. *Mol Genet Metab.* 2011; 104(3):279-283. doi:10.1016/j.ymgme.2011.05.013
30. Ravaglia S., Pichiecchio A., Ponzio M., et al. Changes in skeletal muscle qualities during enzyme replacement therapy in late-onset type II glycogenosis: Temporal and spatial pattern of mass vs. strength response. *J Inherit Metab Dis.* 2010; 33(6):737-745. doi:10.1007/s10545-010-9204-5
31. Wokke J.H.J., Escolar D.M., Pestronk A., et al. Clinical features of late-onset pompe disease: A prospective cohort study. *Muscle Nerve.* 2008; 38(4):1236-1245. doi:10.1002/mus.21025
32. Sechi A., Zuccarelli L., Grassi B., et al. Exercise training alone or in combination with high-protein diet in patients with late onset Pompe disease: Results of a cross over study. *Orphanet J Rare Dis.* 2020; 15(1). doi:10.1186/s13023-020-01416-6
33. Van der Ploeg A.T., Barohn R., Carlson L., et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. *Mol Genet Metab.* 2012; 107(3):456-461. doi:10.1016/j.ymgme.2012.09.015
34. Van Der Ploeg A.T., Clemens P.R., Corzo D., et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *New Engl J Med.* 2010; 362(15):1396-1406. doi:10.1056/NEJMoa0909859
35. Illes Z, Mike A, Trauninger A, Vardi K, Vaczi M. Motor function and respiratory capacity in patients with late-onset pompe disease. *Muscle Nerve.* 2014; 49(4):603-606. doi:10.1002/mus.24142

B. eMethod:

5 Establishing the research question through the P.I.C.O.S. model

The establishment of the research question was carried out with the help of a library methodologist with expertise in documentary research.

- **Population:** Adults with late-onset glycogenosis type 2 or "Pompe disease"
- **Intervention:** Any type of intervention to describe the neuromuscular performance, locomotion and postural control of the study population. Any intervention aimed at comparing the study population with a control population. Any intervention targeting therapeutics to improve neuromuscular performance, locomotion and postural control in the study population.
- **Comparisons:** Healthy population or untreated population or patients baseline values
- **Outcome:** Any outcome assessing neuromuscular performance (for example: Manual muscle testing, dynamometer, Quick Motor Function Test). Any outcome assessing locomotion (for example 6-MWT, 10 m walk test, climb 4-step test, Timed Up and Go test, Walton Gardner Medwin score, biomechanics outcomes). Any outcome assessing postural control (for example center of pressure parameters, center of mass parameters)
- **Study design:** RCT, non-randomized studies of interventions, cohort studies and case controls, cross-sectional studies

6 Exclusion criteria

Only studies producing primary data on at least 4 participants were included, while unpublished work, conference abstracts, poster presentation and gray literature were excluded. Any study in

a language other than English and French is excluded. No restrictions are imposed on the date of publication.

7 Establishing the research equations

The establishment of the search equations was carried out with the help of a library methodologist specializing in documentary research. It was conducted on content published before May 2021 in three international databases: PubMed, Embase, and the Cochrane Library.

Final search equations performed on Embase, PubMed legacy and Cochrane Library.

1. Late-onset Pompe disease equation		
Topic	Key terms	Free words
Pathology	“Glycogen Storage Disease Type II”	“glycogen storage disease type 2” OR “glycogen storage disease type ii” OR “glycogen storage disease, generalized” OR “glycogenosis ii” OR “glycogenosis type 2” OR “acid alpha glucosidase deficiency” OR “acid maltase deficiency disease” OR “alpha-glucosidase deficiency” OR “deficiency of alpha glucosidase” OR “deficiency, gaa” OR “disease, pompe” OR “gaa deficiencies” OR “gaa deficiency” OR “generalized glycogenosis” OR “glycogen storage disease ii” OR “glycogen storage disease type 2” OR “glycogenosis 2” OR “glycogenosis type ii” OR “gsd2” OR “gsd ii” OR “pompe disease” OR “pompe diseases” OR “pompe disease” OR “type ii, glycogenosis”
Equation A: pathology Key terms OR pathology Freewords		
Age	“Adult” OR “Late Onset Disorders”	“late onset pompe disease” OR “glycogen storage disease type ii, adult” OR “late onset pompe disorder” OR “adult” OR “adults” OR “late onset disorder” OR “late onset disorders” OR “middle aged” OR “aged” OR “middle age” OR “young adult” OR “adult, young” OR “aged” OR “elderly” OR “adult pompe disease” OR “adult onset pompe disease” OR “pompe disease adult”
Equation B: age Key terms OR age Freewords		

Equation 1: Equation a AND Equation b.

2. Motor functions equation

Topic	Key terms	Free words
Motor activity	Motor Activity OR Motor Skills OR "Motion"	"motor performance" OR "ability, motor" OR "function, motor" OR "motor ability" OR "motor performance" OR "motor skills" OR "performance, motor" OR "motor activity" OR "motor activity" OR "motion" OR "motion" OR "movement" OR "activities, motor" OR "motor activities" OR "skills, motor" OR "motor movement" OR "activity, motor" OR "motor skill" OR "skill, motor" OR "motor function" OR "motor functions"

Equation C: Motor activity Key terms OR pathology Freewords

Neuromuscular	Neuromuscular Manifestations" OR "Muscular Diseases" OR "Muscle Weakness" OR "Paresis" OR "Muscular Atrophy" OR "Musculoskeletal Abnormalities" OR "Muscle Fatigue" OR "Paralysis"	"muscle disease" OR "muscle defect" OR "muscle disease" OR "muscle disorder" OR "muscle pathology" OR "muscular diseases" OR "muscular disorder" OR "neuromuscular manifestations" OR "muscle weakness" OR "muscle strength loss" OR "muscle weakening" OR "muscle weakness" OR "neuromuscular fatigue" OR "weakness, muscle" OR "musculoskeletal disease" OR "musculoskeletal disease" OR "musculoskeletal diseases" OR "musculoskeletal disorder" OR "musculoskeletal symptom" OR "neuromuscular diseases" OR "neuromuscular disease" OR "neuromuscular disorder" OR "neuromuscular dysfunction" OR "neuromuscular syndrome" OR "neuromyopathy" OR "muscle fatigue" OR "fatigue, muscle" OR "muscle fatigue" OR "muscle fatty infiltration" OR "muscle fatty degeneration" OR "myopathy" OR "myopathies" OR "myopathy" OR "skeletal muscle disease" OR "paralysis" OR "muscle palsy" OR "muscle paralysis" OR "muscular palsy" OR "muscular paralysis" OR "paralysis, muscle" OR "paralytic disease" OR "tardy apoplexy" OR "muscle atrophy" OR "amyotrophia" OR "amyotrophy" OR "atrophy type 2" OR "atrophy, muscle" OR "degeneration, muscle" OR "muscle atrophia" OR "muscle atrophy" OR "muscle cell degeneration" OR "muscle degeneration" OR "muscle fiber atrophy" OR "muscle fiber degeneration" OR
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	OR “Muscular Disorders, Atrophic”	“muscle recession” OR “muscle wasting” OR “muscular atrophy” OR “muscular degeneration” OR “muscular disorders, atrophic” OR “myoatrophy” OR “myodegeneration” OR “myofibrillar degeneration” OR “myophagism” OR “muscle injury” OR “injury, muscle” OR “muscle damage” OR “muscle injury” OR “muscle lesion” OR “muscle trauma” OR “muscular injury” OR “skeletal muscle damage” OR “trauma, muscle” OR “myositis” OR “idiopathic inflammatory myopathy” OR “inflammatory myopathy” OR “muscle infection” OR “muscle inflammation” OR “myopathy, inflammatory” OR “myositis” OR “myositis, allergic” OR “neuromyositis” OR “muscle” OR “muscle tissue” OR “muscles, striated” OR “striated muscles” OR “muscles, skeletal” OR “muscles, voluntary” OR “skeletal muscles” OR “voluntary muscles” OR “muscular weakness” OR “muscular weaknesses” OR “weakness, muscular” OR “fatigue, muscular” OR “muscular fatigue” OR “muscular disease” OR “myopathic condition” OR “myopathic conditions” OR “myopathies” OR “neuromuscular diseases” OR “neuromuscular function” OR “musculoskeletal function”)
Equation D: Key Neuromuscular terms OR pathology Freewords		
Postural control	“Postural Balance” OR “Posture” OR “Standing Position”	“postural control” OR “balance disorder” OR “body equilibrium” OR “center of pressure” OR “center of mass” OR “center of gravity” OR “stability” OR “body position” OR “body posture” OR “position, body” OR “posture” OR “posture, body” OR “abnormal posture” OR “abnormal posturing” OR “postural abnormalities” OR “postural abnormality” OR “balance control” OR “stabilometry” OR “berg balance test” OR “berg balance scale” OR “balance” OR “balance control” OR “stability” OR “postural equilibrium” OR “equilibrium” OR “postural” OR “stabilometry” OR “balance disorder” OR “body positioning” OR “balance, postural” OR “equilibrium, musculoskeletal” OR “equilibrium, postural” OR “musculoskeletal equilibrium” OR “postural equilibrium.”
Equation E: Postural control Key terms OR pathology Freewords		

Gait	“Locomotion” OR “Gait” OR “Gait Disorders, Neurologic” OR “Walking” OR “Walking Speed” OR “Mobility Limitation” OR “Gait Analysis” OR “Walk Test” OR “Spatiotemporal Analysis” OR “Dependent Ambulation”	(“locomotion” OR “behavior, locomotor” OR “locomotion pattern” OR “locomotor behavior” OR “locomotor behavior” OR “locomotor response” OR “motor behavior” OR “motor behavior” OR “walking” OR “forest walking” OR “gait” OR “biped gait” OR “gait analysis” OR “gait training” OR “pattern, walking” OR “walking pattern” OR “gait disorder” OR “abnormal gait” OR “gait deviation” OR “gait deviations” OR “gait disorder” OR “walking parameters” OR “walking parameters” OR “walking difficulty” OR “walking aid” OR “neurologic gait disorder” OR “gait disorders, neurologic” OR “neurologic gait disorder” OR “spatiotemporal analysis” OR “gait analysis system” OR “gaitrite” OR “gait analysis system” OR “walk test” OR “walk test” OR “walking test” OR “walking distance” OR “distance walked” OR “walk distance” OR “walked distance” OR “ambulation” OR “activities, locomotor” OR “activity, locomotor” OR “locomotor activities” OR “locomotor activity” OR “gaits” OR “pace, walking” OR “speed, walking” OR “speeds, walking” OR “walking pace” OR “walking paces” OR “walking speeds” OR “test, walk” OR “tests, walk” OR “walk tests” OR “spatiotemporal pattern” OR “walking distance” OR “spatiotemporal analysis”)
Equation F: Gait Key terms OR pathology Freewords		
Equation 2: (Equation C) OR (Equation D) OR (Equation E) OR (Equation F)		

TOTAL Equation: (Equation 1) AND (Equation 2)

Example on Pubmed:

((((("Glycogen Storage Disease Type II"[Mesh]) OR ("glycogen storage disease type 2" OR "cardiomuscular glycogenosis" OR "diffuse glycogenosis" OR "glycogen storage disease type ii" OR "glycogen storage disease, generalized" OR "glycogenosis ii" OR "glycogenosis type 2" OR "acid alpha glucosidase deficiency" OR "acid maltase deficiency disease" OR "alpha-glucosidase deficiency" OR "deficiency of alpha glucosidase" OR "deficiency, gaa" OR "disease, pompe" OR "gaa deficiencies" OR "gaa deficiency" OR "generalized glycogenoses" OR "generalized glycogenosis" OR "glycogen storage disease ii" OR "glycogen storage disease type 2" OR "glycogenosis 2" OR "glycogenosis type ii" OR "gsd2" OR "gsd ii" OR "pompe disease" OR "pompe diseases" OR "pompes disease" OR "type ii, glycogenosis")))) AND (((("Adult"[Mesh]) OR "Late Onset Disorders"[Mesh])) OR ("late onset

pompe disease" OR *"glycogen storage disease type ii, adult"* OR *"late onset pompe disorder"*
OR *"adult"* OR *"adults"* OR *"grown-ups"* OR *"grownup"* OR *"grownups"* OR *"late onset disorder"* OR *"late onset disorders"* OR *"middle aged"* OR *"aged"* OR *"middle age"* OR
"young adult" OR *"adult, young"* OR *"prime adult"* OR *"prime adults"* OR *"young adults"*
OR *"aged"* OR *"aged patient"* OR *"aged people"* OR *"aged person"* OR *"aged subject"* OR
"elderly" OR *"elderly patient"* OR *"elderly people"* OR *"elderly person"* OR *"elderly sub-
ject"* OR *"senior citizen"* OR *"senium"* OR *"adult pompe disease"* OR *"adult onset pompe
disease"* OR *"pompe disease adult"*)))) AND (((((((("Motor Activity"[Mesh]) OR "Motor
Skills"[Mesh]) OR "Motion"[Mesh])) OR ("motor performance" OR "ability, motor" OR
"function, motor" OR "motor ability" OR "motor performance" OR "motor skills" OR
"performance, motor" OR "motor activity" OR "motor activity" OR "motion" OR "motion"
OR "movement" OR "activities, motor" OR "motor activities" OR "skills, motor" OR "mo-
tor movement" OR "activity, motor" OR "motor skill" OR "skill, motor" OR "motor func-
tion" OR "motor functions")))) OR (((((((("Neuromuscular Manifestations"[Mesh]) OR
"Muscular Diseases"[Mesh]) OR "Muscle Weakness"[Mesh]) OR "Paresis"[Mesh]) OR
"Muscular Atrophy"[Mesh]) OR "Musculoskeletal Abnormalities"[Mesh]) OR "Muscle
Fatigue"[Mesh]) OR "Paralysis"[Mesh]) OR "Muscular Disorders, Atrophic"[Mesh])) OR
("muscle disease" OR "fibromuscular disease" OR "muscle defect" OR "muscle disease"
OR "muscle disorder" OR "muscle pathology" OR "muscular diseases" OR "muscular dis-
order" OR "neuromuscular manifestations" OR "muscle weakness" OR "muscle strength
loss" OR "muscle weakening" OR "muscle weakness" OR "muscular insufficiency" OR
"neuromuscular fatigue" OR "weakness, muscle" OR "musculoskeletal disease" OR "mus-
culoskeletal complaint" OR "musculoskeletal disease" OR "musculoskeletal diseases" OR
"musculoskeletal disorder" OR "musculoskeletal symptom" OR "neuromuscular disease"
OR "neurogenic muscle disease" OR "neurogenic myopathy" OR "neuromuscular disease"
OR "neuromuscular disorder" OR "neuromuscular dysfunction" OR "neuromuscular syn-
drome" OR "neuromyopathy" OR "muscle fatigue" OR "fatigue, muscle" OR "muscle fa-
tigue" OR "muscle fatty infiltration" OR "muscle fatty degeneration" OR "myopathy" OR
"myopathies" OR "myopathies, structural, congenital" OR "myopathy" OR "skeletal mus-
cle disease" OR "paralysis" OR "muscle palsy" OR "muscle paralysis" OR "muscular
palsy" OR "muscular paralysis" OR "myoparalysis" OR "myoplegia" OR "neuromuscular
paralysis" OR "palsy" OR "palsy, muscle" OR "paralysis" OR "paralysis, muscle" OR
"paralytic disease" OR "tardy apoplexy" OR "muscle atrophy" OR "amyotrophia" OR
"amyotrophy" OR "atrophy type 2" OR "atrophy, muscle" OR "degeneration, muscle" OR
"muscle atrophia" OR "muscle atrophy" OR "muscle cell degeneration" OR "muscle de-
generation" OR "muscle fiber atrophy" OR "muscle fiber degeneration" OR "muscle re-
cession" OR "muscle wasting" OR "muscular atrophy" OR "muscular degeneration" OR
"muscular disorders, atrophic" OR "myoatrophy" OR "myodegeneration" OR "myofibril-
lar degeneration" OR "myophagism" OR "muscle injury" OR "injury, muscle" OR "muscle
damage" OR "muscle injury" OR "muscle lesion" OR "muscle trauma" OR "muscular
injury" OR "skeletal muscle damage" OR "trauma, muscle" OR "myositis" OR "idiopathic
inflammatory myopathy" OR "inflammatory myopathy" OR "muscle infection" OR "mus-
cle inflammation" OR "myopathy, inflammatory" OR "myositis" OR "myositis, allergic"
OR "neuromyositis" OR "muscle" OR "muscle tissue" OR "muscles, striated" OR "striated
muscles" OR "muscles, skeletal" OR "muscles, voluntary" OR "skeletal muscles" OR "vol-
untary muscles" OR "muscular weakness" OR "muscular weaknesses" OR "weakness,
muscular" OR "fatigue, muscular" OR "muscular fatigue" OR "muscular disease" OR
"myopathic condition" OR "myopathic conditions" OR "myopathies" OR "neuromuscular
diseases" OR "neuromuscular function" OR "musculoskeletal function")))) OR (((("Pos-

tural Balance"[Mesh]) OR "Posture"[Mesh]) OR "Standing Position"[Mesh])) OR ("postural control" OR "balance disorder" OR "body equilibrium" OR "center of pressure" OR "center of mass" OR "enter of gravity" OR "stability" OR "body position" OR "body posture" OR "position, body" OR "posture" OR "posture, body" OR "abnormal posture" OR "abnormal posturing" OR "postural abnormalities" OR "postural abnormality" OR "balance control" OR "stabilometry" OR "berg balance test" OR "berg balance scale" OR "balance" OR "balance control" OR "stability" OR "postural equilibrium" OR "equilibrium" OR "postural" OR "stabilometry" OR "balance disorder" OR "body positioning" OR "balance, postural" OR "equilibrium, musculoskeletal" OR "equilibrium, postural" OR "musculoskeletal equilibrium" OR "postural equilibrium")) OR (((((((((((("Locomotion"[Mesh]) OR "Gait"[Mesh]) OR "Gait Disorders, Neurologic"[Mesh]) OR "Walking"[Mesh]) OR "Walking Speed"[Mesh]) OR "Mobility Limitation"[Mesh]) OR "Gait Analysis"[Mesh]) OR "Walk Test"[Mesh]) OR "Spatio-Temporal Analysis"[Mesh]) OR "Dependent Ambulation"[Mesh])))) OR ("locomotion" OR "behavior, locomotor" OR "locomotion pattern" OR "locomotor behavior" OR "locomotor behaviour" OR "locomotor response" OR "motor behavior" OR "motor behaviour" OR "walking" OR "forest walking" OR "gait" OR "biped gait" OR "gait analysis" OR "gait training" OR "pattern, walking" OR "walking pattern" OR "gait disorder" OR "abnormal gait" OR "gait deviation" OR "gait deviations" OR "gait disorder" OR "walking parameters" OR "walking parameters" OR "walking difficulty" OR "walking aid" OR "neurologic gait disorder" OR "gait disorders, neurologic" OR "neurologic gait disorder" OR "spatiotemporal analysis" OR "gait analysis system" OR "gaitrite" OR "locometrix" OR "gait analysis system" OR "walk test" OR "walk test" OR "walking test" OR "walking distance" OR "distance walked" OR "walk distance" OR "walked distance" OR "ambulation" OR "activities, locomotor" OR "activity, locomotor" OR "locomotor activities" OR "locomotor activity" OR "gaits" OR "pace, walking" OR "speed, walking" OR "speeds, walking" OR "walking pace" OR "walking paces" OR "walking speeds" OR "test, walk" OR "tests, walk" OR "walk tests" OR "6-minute walk test" OR "endurance shuttle walk test" OR "incremental shuttle walk test" OR "test, 6-minute walk" OR "spatiotemporal pattern" OR "walking distance" OR "spatiotemporal analysis"))))

Final number of articles screened: 2868

- Embase n = 1477
- Pubmed n= 1333
- Cochrane n= 58

8 Manual search

A review of the references in the selected articles allowed us to add 17 additional references.

9 Study selection and synthesis

Search results were treated using CADIMA, a data management portal for evidence synthesis.

The selection of articles was performed in two phases:

(1) selection based on titles and abstracts: Double screening was performed by two independent blind reviewers (TM and TC). Conflicts over data inclusion were resolved by consensus with a third party (CB). 2,157 titles and abstracts were analyzed, 262 were retained for selection phase 2 and 1895 were excluded.

(2) selection based on full texts. Double screening was performed by two independent blind reviewers (TM and TC). Conflicts over data inclusion were resolved by consensus with a third party (CB). 262 full texts were analyzed, 58 were included in the scoping review and 204 were excluded.

Of the excluded full texts, 67 were conference paper or poster report, 26 did not report primary data, 62 focused on other diseases, 41 did not report selected outcomes and 8 studied a sample size of less than 4 patients.

10 Data extraction

Extraction was performed by two independent reviewers (TM and TC). Conflicts over data extractions were resolved by consensus with a third party (CB). Data were extracted into a synthesis table organized into six categories: Authors and publication date, design of study, sample and functional level of the population, purpose of the study, outcome measures and study findings.

Table 1: Summary of data extraction by topic

Authors	Design	Sample	Purpose	Measures	Study findings
(MEAN WGM)					

C. eAppendix:

eAppendix 1: Checklist PRISMA-ScR

Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	RE- PORTED ON PAGE #
TITLE			
Title	1	Identify the report as a scoping review.	1
ABSTRACT			
Structured summary	2	Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives.	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach.	2
Objectives	4	Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives.	3
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address); and if available, provide registration information, including the registration number.	3
Eligibility criteria	6	Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale.	3
Information sources*	7	Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed.	3-4
Search	8	Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	3-4

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	RE- PORTED ON PAGE #
Selection of sources of evidence†	9	State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review.	4
Data charting process‡	10	Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought and any assumptions and simplifications made.	4
Critical appraisal of individual sources of evidence§	12	If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe the methods used and how this information was used in any data synthesis (if appropriate).	4
Synthesis of results	13	Describe the methods of handling and summarizing the data that were charted.	4
RESULTS			
Selection of sources of evidence	14	Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram.	4
Characteristics of sources of evidence	15	For each source of evidence, present characteristics for which data were charted and provide the citations.	4
Critical appraisal within sources of evidence	16	If done, present data on critical appraisal of included sources of evidence (see item 12).	4-10
Results of individual sources of evidence	17	For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives.	4-10
Synthesis of results	18	Summarize and/or present the charting results as they relate to the review questions and objectives.	4-10
DISCUSSION			
Summary of evidence	19	Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups.	10-13
Limitations	20	Discuss the limitations of the scoping review process.	13

SECTION	ITEM	PRISMA-ScR CHECKLIST ITEM	RE-PORTED ON PAGE #
Conclusions	21	Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps.	14
FUNDING			
Funding	22	Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review.	14

JB1 = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.

* Where *sources of evidence* (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.

† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with *information sources* (see first footnote).

‡ The frameworks by Arksey and O'Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.

§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of "risk of bias" (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. *Ann Intern Med*. 2018; 169:467–473. doi: 10.7326/M18-0850.

eAppendix 2 Complete list of articles included by topic

Complete reference list of articles included by topic.

<i>Topics</i>	<i>Number of references</i>	<i>References</i>
Neuromuscular performance	48/58	1–48

Locomotion	52/58	7–47,49–58
Postural control	2/58	47,48

References:

1. De Jager A.E.J., Van Der Vliet T.M., Van Der Ree T.C., Oosterink B.J., Loonen M.C.B. Muscle computed tomography in adult-onset acid maltase deficiency. *Muscle Nerve*. 1998; 21(3):398-400. doi:10.1002/(SICI)1097-4598(199803)21:3<398::AID-MUS15>3.0.CO;2-W
2. De Vries J.M., Van Der Beek N.A., Hop W.C., et al. Effect of enzyme therapy and prognostic factors in 69 adults with Pompe disease: An open-label single-center study. *Orphanet J Rare Dis*. 2012; 7(1). doi:10.1186/1750-1172-7-73
3. Pichiecchio A., Uggetti C., Ravaglia S., et al. Muscle MRI in adult-onset acid maltase deficiency. *Neuromuscular Disord*. 2004; 14(1):51-55. doi:10.1016/j.nmd.2003.08.003
4. Van der Beek N.A.M.E., Hagemans M.L.C., Reuser A.J.J., et al. Rate of disease progression during long-term follow-up of patients with late-onset Pompe disease. *Neuromuscular Disord*. 2009; 19(2):113-117. doi:10.1016/j.nmd.2008.11.007
5. van der Beek NAME, de Vries JM, Hagemans MLC, et al. Clinical features and predictors for disease natural progression in adults with Pompe disease: a nationwide prospective observational study. *Orphanet J Rare Dis*. 2012; 7:88. doi:10.1186/1750-1172-7-88
6. van den Berg L.E.M., Zandbergen A.A., van Capelle C.I., et al. Low bone mass in Pompe disease. Muscular strength as a predictor of bone mineral density. *Bone*. 2010; 47(3):643-649. doi:10.1016/j.bone.2010.06.021
7. Anderson L.J., Henley W., Wyatt K.M., et al. Effectiveness of enzyme replacement therapy in adults with late-onset Pompe disease: results from the NCS-LSD cohort study. *J Inherit Metab Dis*. 2014; 37(6):945-952. doi:10.1007/s10545-014-9728-1
8. Andreassen CS, Schlütter JM, Vissing J, Andersen H. Effect of enzyme replacement therapy on isokinetic strength for all major muscle groups in four patients with Pompe disease—a long-term follow-up. *Molecular Genetics and Metabolism*. 2014; 112(1):40-43. doi:10.1016/j.ymgme.2014.02.015
9. Angelini C, Semplicini C, Tonin P, et al. Progress in Enzyme Replacement Therapy in Glycogen Storage Disease Type II. *Ther Adv Neurol Disord*. 2009; 2(3):143-153. doi:10.1177/1756285609103324
10. Favejee MM, van der Meijden JC, Kruijschaar ME, Rizopoulos D, van der Ploeg AT, Bussmann JBJ. Association of Muscle Strength and Walking Performance in Adult Patients With Pompe Disease. *Phys Ther*. 2018; 98(11):925-931. doi:10.1093/ptj/pty090
11. Fernández-Simón E., Carrasco-Rozas A., Gallardo E., et al. Study of the effect of anti-rhGAA antibodies at low and intermediate titers in late onset Pompe patients treated with ERT. *Mol Genet Metab*. 2019; 128(1-2):129-136. doi:10.1016/j.ymgme.2019.07.013
12. Fernandez-Simon E, Carrasco-Rozas A, Gallardo E, et al. PDGF-BB serum levels are decreased in adult onset Pompe patients. *Sci Rep*. 2019; 9(1):2139. doi:10.1038/s41598-018-38025-0
13. Figueroa-Bonaparte S, Llauger J, Segovia S, et al. Quantitative muscle MRI to follow up late onset Pompe patients: a prospective study. *Sci Rep*. 2018; 8(1):10898. doi:10.1038/s41598-018-29170-7
14. Figueroa-Bonaparte S, Segovia S, Llauger J, et al. Muscle MRI Findings in Childhood/Adult Onset Pompe Disease Correlate with Muscle Function. *PLoS One*. 2016; 11(10):e0163493. doi:10.1371/journal.pone.0163493
15. Filosto M, Cotti Piccinelli S, Ravaglia S, et al. Assessing the Role of Anti rh-GAA in Modulating Response to ERT in a Late-Onset Pompe Disease Cohort from the Italian GSDII Study Group. *Adv Ther*. 2019; 36(5):1177-1189. doi:10.1007/s12325-019-00926-5

16. Harfouche M, Kishnani PS, Krusinska E, et al. Use of the patient-reported outcomes measurement information system (PROMIS®) to assess late-onset Pompe disease severity. *J Patient Rep Outcomes*. 2020; 4(1):83. doi:10.1186/s41687-020-00245-2
17. Harlaar L, Hogrel J.-Y., Perniconi B., et al. Large variation in effects during 10 years of enzyme therapy in adults with Pompe disease. *Neurology*. 2019; 93(19):e1756-e1767. doi:10.1212/WNL.00000000000008441
18. Hundsberger T., Rösler K.M., Findling O. Cessation and resuming of alglucosidase alfa in Pompe disease: a retrospective analysis. *J Neurol*. 2014; 261(9):1684-1690. doi:10.1007/s00415-014-7402-z
19. Illes Z, Mike A, Trauninger A, Vardi K, Vaczi M. Motor function and respiratory capacity in patients with late-onset pompe disease. *Muscle Nerve*. 2014; 49(4):603-606. doi:10.1002/mus.24142
20. Khan A.A., Boggs T., Bowling M., et al. Whole-body magnetic resonance imaging in late-onset Pompe disease: Clinical utility and correlation with functional measures. *J Inherit Metab Dis*. 2020; 43(3):549-557. doi:10.1002/jimd.12190
21. Koeberl D.D., Austin S., Case L.E., et al. Adjunctive albuterol enhances the response to enzyme replacement therapy in late-onset Pompe disease. *FASEB J*. 2014; 28(5):2171-2176. doi:10.1096/fj.13-241893
22. Koeberl D.D., Case L.E., Smith E.C., et al. Correction of Biochemical Abnormalities and Improved Muscle Function in a Phase I/II Clinical Trial of Clenbuterol in Pompe Disease. *Mol Ther*. 2018; 26(9):2304-2314. doi:10.1016/j.ymthe.2018.06.023
23. Koeberl DD, Case LE, Desai A, et al. Improved muscle function in a phase I/II clinical trial of albuterol in Pompe disease. *Mol Genet Metab*. 2020; 129(2):67-72. doi:10.1016/j.ymgme.2019.12.008
24. Kuperus E., Kruijshaar M.E., Wens S.C.A., et al. Long-term benefit of enzyme replacement therapy in Pompe disease: A 5-year prospective study. *Neurology*. 2017; 89(23):2365-2373. doi:10.1212/WNL.0000000000004711
25. Laforêt P., Laloui K., Granger B., et al. The French Pompe registry. Baseline characteristics of a cohort of 126 patients with adult Pompe disease. *Rev Neurol*. 2013; 169(8-9):595-602. doi:10.1016/j.neurol.2013.07.002
26. Laforêt P., Nicolino M., Eymard B., et al. Juvenile and adult-onset acid maltase deficiency in France: Genotype-phenotype correlation. *Neurology*. 2000; 55(8):1122-1128. doi:10.1212/WNL.55.8.1122
27. Lollert A., Stihl C., Hötter A.M., et al. Quantification of intramuscular fat in patients with late-onset Pompe disease by conventional magnetic resonance imaging for the long-term follow-up of enzyme replacement therapy. *PLoS ONE*. 2018; 13(1). doi:10.1371/journal.pone.0190784
28. Nuñez-Peralta C., Alonso-Pérez J., Llauger J., et al. Follow-up of late-onset Pompe disease patients with muscle magnetic resonance imaging reveals increase in fat replacement in skeletal muscles. *J Cachexia Sarcopenia Muscle*. 2020;(Nuñez-Peralta C.; Llauger J.; Martínez-Noguera A.) Radiology Department, Hospital de la Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Barcelona, Spain). doi:10.1002/jcsm.12555
29. Pellegrini N., Laforet P., Orlikowski D., et al. Respiratory insufficiency and limb muscle weakness in adults with Pompe's disease. *Eur Respir J*. 2005; 26(6):1024-1031. doi:10.1183/09031936.05.00020005
30. Pena L.D.M., Barohn R.J., Byrne B.J., et al. Safety, tolerability, pharmacokinetics, pharmacodynamics, and exploratory efficacy of the novel enzyme replacement therapy avalglucosidase alfa (neoGAA) in treatment-naïve and alglucosidase alfa-treated patients with late-onset Pompe disease: A phase 1, open-label, multicenter, multinational, ascending dose study. *Neuromuscular Disord*. 2019; 29(3):167-186. doi:10.1016/j.nmd.2018.12.004
31. Ravaglia S., Pichiecchio A., Ponzio M., et al. Changes in skeletal muscle qualities during enzyme replacement therapy in late-onset type II glycogenosis: Temporal and spatial pattern of mass vs. strength response. *J Inherit Metab Dis*. 2010; 33(6):737-745. doi:10.1007/s10545-010-9204-5
32. Regnery C, Kornblum C, Hanisch F, et al. 36 months observational clinical study of 38 adult Pompe disease patients under alglucosidase alfa enzyme replacement therapy. *J Inherit Metab Dis*. 2012; 35(5):837-845. doi:10.1007/s10545-012-9451-8
33. Rehmann R, Froeling M, Rohm M, et al. Diffusion tensor imaging reveals changes in non-fat infiltrated muscles in late onset Pompe disease. *Muscle Nerve*. Published online 2020. doi:10.1002/mus.27021

34. Scheidegger O., Leupold D., Sauter R., Findling O., Rösler K.M., Hundsberger T. 36-Months follow-up assessment after cessation and resuming of enzyme replacement therapy in late onset Pompe disease: data from the Swiss Pompe Registry. *J Neurol.* 2018; 265(12):2783-2788. doi:10.1007/s00415-018-9065-7
35. Sechi A., Zuccarelli L., Grassi B., et al. Exercise training alone or in combination with high-protein diet in patients with late onset Pompe disease: Results of a cross over study. *Orphanet J Rare Dis.* 2020; 15(1). doi:10.1186/s13023-020-01416-6
36. Slonim A.E., Bulone L., Goldberg T., et al. Modification of the natural history of adult-onset acid maltase deficiency by nutrition and exercise therapy. *Muscle Nerve.* 2007; 35(1):70-77. doi:10.1002/mus.20665
37. Stepien K.M., Hendriksz C.J., Roberts M., Sharma R. Observational clinical study of 22 adult-onset Pompe disease patients undergoing enzyme replacement therapy over 5 years. *Mol Genet Metab.* 2016; 117(4):413-418. doi:10.1016/j.ymgme.2016.01.013
38. Strothotte S., Strigl-Pill N., Grunert B., et al. Enzyme replacement therapy with alglucosidase alfa in 44 patients with late-onset glycogen storage disease type 2:12-month results of an observational clinical trial. *J Neurol.* 2010; 257(1):91-97. doi:10.1007/s00415-009-5275-3
39. Terzis G., Dimopoulos F., Papadimas G.K., et al. Effect of aerobic and resistance exercise training on late-onset Pompe disease patients receiving enzyme replacement therapy. *Mol Genet Metab.* 2011; 104(3):279-283. doi:10.1016/j.ymgme.2011.05.013
40. Van Den Berg L.E.M., Favejee M.M., Wens S.C.A., et al. Safety and efficacy of exercise training in adults with Pompe disease: Evaluation of endurance, muscle strength and core stability before and after a 12 week training program. *Orphanet J Rare Dis.* 2015; 10(1). doi:10.1186/s13023-015-0303-0
41. Van der Ploeg A.T., Barohn R., Carlson L., et al. Open-label extension study following the Late-Onset Treatment Study (LOTS) of alglucosidase alfa. *Mol Genet Metab.* 2012; 107(3):456-461. doi:10.1016/j.ymgme.2012.09.015
42. Van Der Ploeg A.T., Clemens P.R., Corzo D., et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. *New Engl J Med.* 2010; 362(15):1396-1406. doi:10.1056/NEJMoa0909859
43. van der Ploeg A., Carlier PG, Carlier RY, et al. Prospective exploratory muscle biopsy, imaging, and functional assessment in patients with late-onset Pompe disease treated with alglucosidase alfa: The EMBASSY Study. *Mol Genet Metab.* 2016; 119(1-2):115-123. doi:10.1016/j.ymgme.2016.05.013
44. Vanherpe P., Fieuws S., D'Hondt A., et al. Late-onset Pompe disease (LOPD) in Belgium: Clinical characteristics and outcome measures. *Orphanet J Rare Dis.* 2020; 15(1). doi:10.1186/s13023-020-01353-4
45. Wokke J.H.J., Escolar D.M., Pestronk A., et al. Clinical features of late-onset pompe disease: A prospective cohort study. *Muscle Nerve.* 2008; 38(4):1236-1245. doi:10.1002/mus.21025
46. Yuan M, Andrinopoulou ER, Kruijshaar ME, et al. Positive association between physical outcomes and patient-reported outcomes in late-onset Pompe disease: a cross sectional study. *Orphanet J Rare Dis.* 2020; 15(1):232. doi:10.1186/s13023-020-01469-7
47. Schneider I, Zierz S, Schulze S, et al. Characterization of Gait and Postural Regulation in Late-Onset Pompe Disease. *Applied Sciences.* 2020; 10(19):7001. doi:10.3390/app10197001
48. Valle M.S., Casabona A., Fiumara A., Castiglione D., Sorge G., Cioni M. Quantitative analysis of upright standing in adults with late-onset Pompe disease. *Sci Rep.* 2016; 6((Valle M.S.; Casabona A.; Cioni M.) Gait and Posture Analysis Laboratory, Department of Biomedical and Biotechnological Sciences, University of Catania, Catania, Italy):37040. doi:10.1038/srep37040
49. Alandy-Dy J, Wencel M, Hall K, et al. Variable clinical features and genotype-phenotype correlations in 18 patients with late-onset Pompe disease. *Ann Transl Med.* 2019; 7(13):276. doi:10.21037/atm.2019.06.48
50. Angelini C, Semplicini C, Ravaglia S, et al. Observational clinical study in juvenile-adult glycogenosis type 2 patients undergoing enzyme replacement therapy for up to 4 years. *J Neurol.* 2012; 259(5):952-958. doi:10.1007/s00415-011-6293-5
51. Angelini C, Semplicini C, Ravaglia S, et al. New motor outcome function measures in evaluation of late-onset Pompe disease before and after enzyme replacement therapy. *Muscle Nerve.* 2012; 45(6):831-834. doi:10.1002/mus.23340

52. Bembi B., Pisa F.E., Confalonieri M., et al. Long-term observational, non-randomized study of enzyme replacement therapy in late-onset glycogenosis type II. *J Inherit Metab Dis.* 2010; 33(6):727-735. doi:10.1007/s10545-010-9201-8
53. McIntosh P.T., Case L.E., Chan J.M., Austin S.L., Kishnani P. Characterization of gait in late onset Pompe disease. *Mol Genet Metab.* 2015; 116(3):152-156. doi:10.1016/j.ymgme.2015.09.001
54. Müller-Felber W, Horvath R, Gempel K, et al. Late onset Pompe disease: Clinical and neurophysiological spectrum of 38 patients including long-term follow-up in 18 patients. *Neuromuscular Disorders.* 2007; 17(9):698-706. doi:10.1016/j.nmd.2007.06.002
55. Ripolone M, Violano R, Ronchi D, et al. Effects of short-to-long term enzyme replacement therapy (ERT) on skeletal muscle tissue in late onset Pompe disease (LOPD). *Neuropathol Appl Neurobiol.* 2018; 44(5):449-462. doi:10.1111/nan.12414
56. Starbuck C, Reay J, Silk E, Roberts M, Hendriksz C, Jones R. Are there common walking gait characteristics in patients diagnosed with late-onset Pompe disease? *Human Movement Science.* 2021; 77:102777. doi:10.1016/j.humov.2021.102777
57. Semplicini C, De Antonio M, Taouagh N, et al. Long-term benefit of enzyme replacement therapy with alglucosidase alfa in adults with Pompe disease: Prospective analysis from the French Pompe Registry. *J Inherit Metab Dis.* Published online 2020. doi:10.1002/jimd.12272
58. Witkowski G, Konopko M, Rola R, Lugowska A, Ryglewicz D, Sienkiewicz-Jarosz H. Enzymatic replacement therapy in patients with late-onset Pompe disease - 6-Year follow up. *Neurol Neurochir Pol.* 2018; 52(4):465-469. doi:10.1016/j.pjnns.2018.05.002